DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 23 1998

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The Honorable Kay Bailey Hutchison
United States Senator
10440 North Central Expressway
Suite 1160
LB 606
Dallas, Texas 75231

Dear Senator Hutchison:

This is in further response to your letter of February 18, 1998, on behalf of Mr. Ralph Oats of Wellness International Network, Ltd., Carrollton, Texas, regarding the Food and Drug Administration's (FDA or the Agency) proposed rule on dietary supplements containing ephedrine alkaloids (62 FR 30678).

The proposed rule would establish requirements for the formulation and labeling of dietary supplements containing ephedrine alkaloids. The ephedrine alkaloids in dietary supplements (ephedrine, psuedoephedrine, norephedrine, methylephedrine, norpseudoephedrine, methylpseudoephedrine, and related alkaloids) are naturally occurring stimulants and are usually derived from one of several species of herbs of the genus Ephedra, sometimes called Ma huang, Chinese Ephedra, and epitonin. In the proposed rule, the Agency is proposing to:

- make a finding, which would have the force and effect of law, that a dietary supplement is adulterated if it contains 8 milligrams (mg) or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in intake of 8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids;

- require that the label of dietary supplements that contain ephedrine alkaloids state "Do not use this product for more than 7 days";

- prohibit the use of ephedrine alkaloids with ingredients, or with ingredients that contain substances, that have a known stimulant effect (e.g., sources of caffeine or yohimbine);

- prohibit labeling claims that require long-term intake to achieve the purported effect (e.g., weight loss and body building);

95N-0304

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- require a statement in conjunction with claims that encourage short-term excessive intake to enhance the purported effect (e.g., energy) that "Taking more than the recommended serving may result in heart attack, stroke, seizure or death"; and

- require specific warning statements to appear on product labels.

The proposal also articulates FDA's policy that products marketed as alternatives to illicit street drugs are drugs, not dietary supplements.

FDA proposed this rule in response to serious illnesses and injuries associated with the use of dietary supplement products that contain ephedrine alkaloids and in response to the Agency's investigations and analyses of these illnesses and injuries. Reported adverse events range from episodes of high blood pressure, irregularities in heart rate, insomnia, nervousness, tremors, and headaches, to seizures, heart attacks, strokes, and death. As of January 1997, FDA had received over 800 reports of adverse events associated with the use of more than 100 different dietary supplement products that contained, or were suspected of containing, ephedrine alkaloids. The adverse events reports showed consistent patterns of illness and injury among otherwise healthy individuals and those with underlying diseases or conditions and are consistent with the effects known and expected to occur with the use of sympathomimetic agents, such as the ephedrine alkaloids. The ephedrine alkaloids are amphetamine-like compounds with potentially strong stimulant effects on the cardiovascular (heart and blood vessels) and nervous systems. Since the publication of the proposed rule, FDA has continued to receive additional reports of adverse events associated with the use of these products.

The proposed measures were developed based on FDA's review of its adverse event reports, the scientific literature, and public comments reviewed by the Agency, including comments generated by an October 1995 advisory working group public meeting and an August 1996 public meeting of FDA's Food Advisory Committee. These experts suggested a number of steps the Agency might take to reduce injuries associated with the use of dietary supplements containing ephedrine alkaloids. The purpose of the proposed rule is to reduce the risk of adverse events for consumers who use these products.

FDA allowed a 75-day comment period on the proposed rule. On September 18, 1997, FDA announced that the comment period would be reopened for an additional 75 days (62 FR 48968). Comments

received in response to the proposal are available for public examination in public docket No. 95N-0304 located in the Dockets Management Branch office. FDA is now evaluating its tentative conclusions in light of comments received on the proposed rule, including the comment enclosed with Mr. Oats' letter.

We hope this information is helpful. If we may be of any further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure
Mr. Oats' correspondence

cc: Dockets Management Branch
(Docket No. 95N-0304)

KH

KAY BAILEY HUTCHISON
TEXAS

COMMITTEES:
APPROPRIATIONS
COMMERCE, SCIENCE,
AND TRANSPORTATION
RULES AND ADMINISTRATION

United States Senate

WASHINGTON, DC 20510–4304

February 18, 1998

RESPECTFULLY REFERRED TO:

Congressional Liaison
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir/Madam:

The attached communication was forwarded to Senator Hutchison by a constituent who is concerned about a matter that falls within you agency's jurisdiction. I would appreciate it if appropriate inquiries could be initiated on this individual's behalf, and if a full response could be prepared for me to report to the constituent.

It would be very helpful if the attached were to accompany your response. In the event you require more information, please do not hesitate to contact me in Dallas at (214)361-3500.

Thank you for your courtesy.

PLEASE REPLY TO:

Office of Senator Kay Bailey Hutchison
Attention: Mary Fae Kamm
10440 North Central Expressway, Suite 1160
LB 606
Dallas, Texas 75231

Enclosure

No. 98-1656

Wellness International Network, Ltd.

February 12, 1998

The Honorable Kay Bailey Hutchinson
United States Senator
10440 North Central Expressway
Suite 1160
Dallas, Texas 75231

Dear Senator Hutchinson:

As a successful Dallas businessman and member of the Republican Eagles, the Republican Presidential Roundtable and the Friends of Phil Gramm Committee, I am writing to you today concerning an issue that merits your immediate consideration and action.

The enclosed docket was submitted to the Food and Drug Administration on December 2, 1997, by the Ad Hoc Committee for Dietary Supplement Safety. In lieu of the FDA's proposal to regulate dietary supplements containing ephedrine alkaloids, I ask that you review these extensive, well-argued and science-based comments opposing the FDA's unjust position.

For over three years, the Ad Hoc Committee has been on the forefront of this opposition, developing and disseminating scientific information disputing the non-science-based, and thus unreasonable, state and federal efforts to regulate dietary supplements made from the herbal plant ephedra. Their ongoing efforts prove that the FDA has ignored scientific literature and other sources showing ephedra herb supplements to be safe at customary commercial doses.

And while Wellness International Network, Ltd. has always supported the FDA in their attempts to keep consumable products safe by providing *reasonable* industry standards, I would be remiss if I failed to mention that if regulations such as these – which involve the livelihood and health of so many thousands of people – are decided on anything *other* than legitimate, scientific evidence, it would be a travesty of the system for which the FDA was intended.

It is our fondest desire to see government and private industry work together for the single purpose of mutual benefit. I would appreciate your support in this matter and look forward to your response.

Sincerely,

Ralph Oats

Ralph Oats

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David Litell, Chairman
William D. Appler, M.A., Executive Director

December 2, 1997

Dockets Management Branch (HFA-305)
Food and Drug Administration
12410 Parklawn Drive, Room 1-23
Rockville, MD 20857

Re: Docket No. 95N-0304:
Proposed Rule: Dietary Supplements
Containing Ephedrine Alkaloids

Dear Sir or Madam:

These comments opposing the Proposed Rule to regulate Dietary Supplements Containing Ephedrine Alkaloids are filed by and on behalf of the Ad Hoc Committee for Dietary Supplement Safety ("the Ad Hoc Committee") which, over the past three years, has taken the leading role in opposing non-science-based, and thus unreasonable, state and federal efforts to regulate dietary supplements made from the herbal plant ephedra.[1]

The Ad Hoc Committee's scientific activities in support of the safety of ephedra herb dietary supplements[2] have been supported by individual consumers and marketers, scientists, and

[1] The Ad Hoc Committee opposes the substantive limitations in the proposal, but in general supports appropriate warning labeling, as discussed below.

[2] The Ad Hoc Committee commissioned two extensive scientific literature reviews, one of which was prepared under the supervision of Rob McCaleb, a member of the Commission on Dietary Supplement Labeling, and written by Dr. Steven Dentali, a member of the FDA's Food Advisory Committee Working Group on ephedra herbal dietary supplements. Both reviews concluded that at commercially recommended dosages, up to 25 mg three to four times per day, these dietary supplements were safe. Our members also conducted detailed animal (rat, mouse, dog) studies on a typical ephedra/caffeine combination dietary supplement in 1995; these showed a wide margin of safety for human use. Our toxicologists [fn. cont.]

over 40 manufacturers and distributors of ephedra herb dietary supplements.[3] The Ad Hoc Committee is thus the largest and longest-operating group developing and disseminating scientific information showing that ephedra herb products are safe as customarily used in the United States.

We have organized our comments in opposition to the Proposed Rule as follows. First, we set out, in an Introduction and Summary, the failure of the agency to employ anything resembling a scientific method in addressing the safety of ephedra herb supplements. In particular, we show that FDA ignored the scientific literature and other sources showing ephedra herb supplements are safe at customary commercial doses; failed to critically evaluate the anecdotal, alleged adverse events[4]; and, most importantly, completely failed to show that individuals who consume ephedra herb supplements incur any more (or greater) adverse events than those who do not. Such a showing is the cornerstone of proving that a substance is hazardous, or helpful, and FDA did not even attempt it.

Second, we discuss the known and accepted scientific evidence concerning the safety of ephedrine alkaloids, which was available to, but completely ignored by, the agency at the time it received the first, heavily solicited, reports of adverse events allegedly caused by the ephedrine

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[fn. cont.] reviewed all the adverse event reports from Texas and the FDA, pointing out their inconsistencies with accepted pharmacokinetic and toxicological principles. In particular, we showed that there was no basis for concluding ephedra herb products were the cause of several deaths accepted by FDA. Our members and others are presently conducting several human clinical trials involving ephedra hereby dietary supplements. Data to date from these trials strongly suggests the absence of any hazard in carefully monitored clinical settings at customary dosage levels or slightly above. The Ad Hoc Committee submitted a 1500-page scientific report to FDA in mid-1995; however, there is no reference to this report in the Proposal. We presented our scientific findings to the FDA working Group in October 1995, distributing our report to each member after FDA failed to do so; and to the Food Advisory Committee in August, 1996.

[3] Those companies which have supported the Committee include: Achievers, NutriSystem, Nutratech, Garden State, Wellness, Natural Balance, Chemins, E'Ola, Alliance, Amrion, Shaperight, Market America, Nature's Sunshine, Omnitrition, Twin Labs, Hammer, Enrich, East Earth, Metabolife, MTM Marketing, Herb Source, Sportron, Metaphysique, Bright Futures, Neturaceutical Corp, Ultimate Nutrition, Affiliated, Dandy Day, 3-D, China Tech, Weinstein Nutritional, Crestmont, Crystal Star, Natrol, HerbPharm, Harker, Threshold, Slim for Life, Gold-N Nutrition, AR2000, and Herbal Science. These companies account for a very substantial amount of the sales of ephedra herb dietary supplements in the United States. This Proposal, if adopted in anything resembling its present form, would wreck havoc with them, driving some of these companies out of business.

[4] FDA counted at least nine AER's where the person did not consume any ephedra product, and it accepted as true claims that ephedra herb consumption caused such clearly unrelated illnesses as Lou Gehrig's disease, MS, late menstruation, and pregnancy. The adverse events of death included one individual killed in an auto accident, and another who was shot. The anecdotal sweeper brings up a great deal of trash, and any unbiased public health agency must discard it, even if the result is that its raw "numbers" look less significant.

alkaloids in ephedra herbal supplements.[5] We show that in light of this overwhelming, existing evidence of safety of these dietary supplements at customary ingestion levels, there was no basis for FDA to assume that a tiny handful of anecdotal cases (approximately 800 in total, from about 20-32 million consumers) reflected any health risk. Besides, as we also show in this section, the adverse effect reports, when analyzed, show almost no cases where any injury is a likely result of consumption of ephedra at a customary, labeled dose.

Third, we show that in light of the science of ephedra herb, there is no substantial support for the specific requirements of the proposal: (1) a dose limitation of less than 8 mg per serving, for three times a day, which is only one-sixth of the OTC ephedrine alkaloid dose found to be safe for health-compromised asthmatics; (2) a seven-day use limit, at this minuscule dosage, when none of the various ephedrine alkaloids that are ubiquitous in OTC drugs were found to require such limitation by the panels of experts and FDA which reviewed their pharmacology[6]; and (3) the exclusion of caffeine from ephedra dietary supplements, when dozens of clinical studies of ephedrine/caffeine combinations show their safety, and FDA does not require the listing of caffeine as counterindicated on OTC drugs containing the same or related ingredients. In brief, there is absolutely no scientific evidence behind any of these three proposals – and the proposed seven-day use limit is contradicted by the To, Gaultieri, and Van Mieghem articles on which it expressly rests.

Fourth, we conclude from the abundant evidence of safety, and the absence of anything other than "political science" supporting the FDA's proposal, that the Proposal should probably be withdrawn. While the proposed "WARNING" labeling is not unreasonable on its face, if these warnings are necessary for anyone consuming essentially any amount of ephedrine alkaloids, the agency should repropose the regulation, to include all OTC drugs containing ephedrine, and related alkaloids such as pseudoephedrine and PPA, rather than singling out ephedra herb dietary supplements for such warnings.

If any dose limitation is established, it should be 25 mg per dose, up to four times per day, which is still only two thirds of the maximum safe OTC dose level, 21 C.F.R. Part 341, and one third of the maximum safe level set in Goodman & Gilman. No time limitation on use should be set; no labeling limitations for weight loss or body building should be adopted; and no prohibition

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[5] Ephedra herb dietary supplements contain 6-8% ephedrine alkaloids. For convenience, we refer to the products as ephedra.

[6] The only purpose of the seven-day limit is to prohibit the structure and function claim of weight loss, the primary use for ephedra herb dietary supplements. In practice, it is a way of removing these supplements from the market without banning them, a power FDA lacks under DSHEA. Since this time limit is unsupported, so would be any limitations upon claims which require more than seven days' use (e.g., weight loss).

on combination with caffeine is necessary.

I. Introduction and Summary: The Proposal Does Not Reflect Accepted Scientific Methodology.

There is an accepted scientific methodology, regularly applied by the agency, to determine whether, and at what level, any food additive, new dietary supplement ingredient, OTC or prescription drug, or biological, may be hazardous to human health. The tenets of this methodology include:

- Review of the existing scientific literature on the substance, to determine what is known about the chemical's risk, particularly at the dose level it is to be used;
- Review of any clinical studies involving the substance;
- Review of available animal studies on the substance and, if necessary, the conduct of additional studies;
- Review of any alleged adverse events caused by the substance, and particularly close review where the adverse events are inconsistent with the literature and animal studies;
- Determination of whether individuals who consume the products suffer a statistically significantly greater number of adverse (or beneficial) events than those who do not.

It is the substance of this opposition to the Proposal that CFSAN did not follow any of these central tenets of toxicology, and that there is thus no scientific basis for its proposals to limit consumption to less than 8 mg per serving, to prohibit consumption for more than a week, and to exclude caffeine from ephedra herb dietary supplements.[7]

First, the literature on ephedrine alkaloids is extensive, and overwhelmingly positive, demonstrating that single doses of ephedrine "up to 60 mg generally do not increase blood pressure [and doses of] 60 or 90 mg of ephedrine . . . produced only small increases in heart rate."[8] As the "Bible" of Toxicology, Goodman and Gilman's The Pharmaceutical Basis of Therapeutics (1990 ed.), confirms, the safe level of ephedrine alkaloids (used in a health-

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[7] Thus, the Proposal embodies not good science, but instead "political" science. It reflects the agency's continuing hostility to herbal dietary supplements, notwithstanding DSHEA, as well as its efforts to influence the public, and then Congress, to amend this Act. See, e.g., the agency's comment that under DSHEA, "if Socrates were to take hemlock, we couldn't do anything about it until he actually drank it," a substantial distortion of FDA's authority.

[8] Pentel, "Toxicity of Over-the-Counter Stimulants", JAMA, 252: 1898-1903 (1984) (Ref. 44).

challenged, asthmatic population) is "25-50 mg every four to six hours," or up to 300 mg a day.[9]

Yet CFSAN did not conduct a competent, comprehensive literature review of ephedra and ephedrine alkaloids, before proposing this action. Instead, it went out of its way to find, and include in its highly selective "References," a few outdated articles (primarily case reports) involving anecdotal responses to ephedrine alkaloids. See, e.g., Refs. 5 (Chen, 1930), 72 (Hirsch, 1965), 86 (Herridge, 1968), 102 (Chopra, Indian Medical Gazette, 1933), 103 (Balyeat, 1932), 104 (Wu, 1927).

The agency fails to cite in its References – and, based upon its preamble, failed to consider – dozens and dozens of relevant articles and clinical trials from the scientific literature which are favorable to the safety of ephedrine alkaloids at 25 mg on less per single dose. Virtually all of these articles were cited, and provided in hard copy, to FDA as part of the Ad Hoc Committee's submissions in July and October, 1995.[10]

Significantly, FDA did not cite, nor include in its list of references, the two clinical papers on which its decision to find that ephedrine alkaloids at 25 mg dose, 150 mg day, were safe, and to reject allegations (similar to those now made by FDA) that such a dosage was unsafe, was based. 41 Fed. Reg. 38312, 38370 (September 9, 1976, Proposed Monograph); 51 Fed. Reg. 35326, 35331 (October 2, 1986, Final Monograph).[11]

Finally, the FDA overlooked both of the comprehensive literature reviews, exceeding one hundred pages of text with over 200 citations and articles attached, prepared by highly qualified, independent experts retained by the Ad Hoc Committee.[12] These unrebutted literature reviews reflect the scientific consensus on ephedrine alkaloids – that they are safe at 25 my dose levels – and thus completely undermine the Proposal.

Second, it is widely accepted, including acceptance by FDA (see the CFSAN Red Book), that studies in animals are appropriate to assist in evaluating the safety of food ingredients. Thus, for example, in the early 1970's, when the chronic safety of the color additive FD&C Red No. 2

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[9] Goodman & Gilman, infra, at pp. 213-214.

[10] Significantly, these favorable materials were not presented in August, 1996, to the Food Advisory Committee. Instead, the members were exposed only to the agency's version of the science, almost entirely based on the anecdotal adverse events, and never peer reviewed.

[11] The articles are Dulfano, et al., "Evaluation of a New . . . [Drug] in Bronchial Asthma . . . Oral Comparison with Ephedrine," Current Therapeutic Research, 15:150-157 (1973); Tashkin et al., "Double-Blind Comparison of Acute Bronchial and Cardiovascular Effects of Oral Terbutaline and Ephedrine", Chest, 68: 155-171 (1975), cited at 41 Fed. Reg. 38371 (Tab 17).

[12] One literature review was done by experts the agency would agree are very well qualified: it was under the direction of a member of the Committee on Dietary Supplement Labeling, and researched by a member of the Food Advisory Committee Working Group.

was at issue, FDA conducted its own lifetime study in rats and mice to attempt to resolve that issue. The agency has also encouraged, and then reviewed, industry-conducted studies for, among others, FDF&C Red No. 4, acrylonitrile, and artificial sweeteners.

However, once again, the agency has ignored extensive animal testing of ephedrine alkaloids. This is surprising because the testing was initially done under the National Toxicology Program, i.e., by the government itself. These 1986 studies showed that a lethal dose of ephedrine alkaloids for most animal species, translated into human consumption, was between 200-400 25 mg tablets, and for the most sensitive species (the mouse), it was 40-80 tablets.[13]

In addition, the Ad Hoc Committee did what FDA should have done when concerns were raised about ephedra herb's safety. It sponsored acute and sub-acute animal studies (rat, mice, dog), testing a typical ephedra herb dietary supplement (Metabolife), which contained ephedra (12 mg ephedrine alkaloids) and 40 mg caffeine.

The results showed, according to the independent toxicologist who reviewed these animal studies, Wayne Snodgrass, M.D., Ph. D., an employee of the State of Texas and then Director of the Texas Poison Control Centers, that ephedra "does not pose any known unreasonable health risks to the general population in its availability as an herbal product." Ibid., Appendix III, C. (Tab 12). Other animal studies reach a similar conclusion, (Tab 12); no animal study suggests that ephedra or ephedrine alkaloids would be harmful at human doses of 25 mg single doses.

Third, the Proposal's finding that 8 mg single doses, up to three times a day, create a hazard to health, is absolutely inconsistent with the OTC Bronchodilator Monograph finding that 25 mg single doses, up to 6 times a day are safe, even for health compromised asthmatics. 21 C.F.R. Part 341. It is impossible for an 8 mg dose of ephedrine alkaloids to be hazardous, where the agency and its outside experts have already found 25 mg single doses to be safe.

This is true because the body does not know whether the ephedrine it consumes is labeled for OTC drug use, or for dietary supplement use. But the body does know that 25 mg is more than three times the supposedly hazardous 8 mg dose, and other things being equal, if the higher dose is safe, so is the lower one. FDA has never offered any explanation of its inconsistency between the higher safe dose and the lower "hazardous" dose; apparently, for the agency, "the dose does not make the poison."[14]

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[13] Summaries of the animal tests are contained in the Ad Hoc Committee's submission to the Food Advisory Committee, August, 1996, Appendix Volume III, Tabs A-D (Tab 12).

[14] A perspicacious member of the Food Safety Committee asked the agency to explain why it had essentially no adverse events reported from the widespread bronchodilator use at 25 mg single doses, but alleged so many such events from very low dietary supplement uses. Dr. Lori Love replied that the "drug and food reporting systems were different." (See Ref. 25). If anything, however, the more advanced drug reporting system should more accurately track AER's, so this answer is either non-responsive or a non-sequitar. In fact, as many of the AER's show, FDA's and the State of Texas's encouraging and stimulating reports of injuries from ephedra herb dietary supplements, accounts for the large [fn. cont.]

Moreover, FDA's expert panel, and the agency itself, concluded that ephedrine alkaloids were safe at 25 mg per single dose, up to six doses per day, in the face of arguments that ephedrine had "effects both on the brain (central) and on nerve endings (peripheral) . . . [including] rapid heartbeat accompanied usually by some elevation of blood pressure." 41 Fed. Reg. at 38370. It rejected these arguments, based upon the clinical studies (cited above and confirmed on Tab 17), which FDA has ignored in this proposal. Yet the OTC preamble, FDA stated:

> However, a study by Dulfano and Glass on 26 asthmatics between the ages of 28 and 61 years showed a single dose of 25 mg had no significant effect on either heart rate or blood pressure. Another recent study of the cardiovascular effects of 25 mg ephedrine in 20 asthmatics showed there was only a modest increase in heart rate up to 11 beats per minute as a maximum, and the systolic and diastolic blood pressure showed no significant change.

41 Fed. Reg. at 38370. Even an overdose, the Panel found, would be self-limiting and thus unlikely to lead to serious medical problems. Ibid.

The Panel concluded that the only side effects of 25 mg doses of ephedrine alkaloids up to six times daily were generally mild: "[n]ervousness, tremor, sleeplessness, nausea, and loss of appetite may occur." 41 Fed. Reg. at 38422. The only potentially "dangerous" side effects would occur solely in "patients taking drugs containing . . . MAO inhibitors." 41 Fed. Reg. at 38370-38371.[15]

Given the extensive clinical and scientific literature that ephedrine alkaloids are safe for use at 25 mg single doses/150 mg daily doses, the National Toxicology Program's and other ephedrine animal studies, the OTC monograph safety finding and supporting materials[16], the Proposal's statement that there is a "virtual absence of publicly available safety data on these supplements" (62 Fed. Reg. at 30679) is at best bizarre. Indeed, it is the existence of this data, showing that these doses of ephedra herb supplements would be expected to be safe, which

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[fn. cont.] number of AER's for these products, along with the agency's failure to purge complaints which are medically impossible, fanciful, or do not involve products containing ephedra.

[15] The agency finalized the OTC bronchodilator regulations essentially as the panel had suggested. In the face of an allegation of one death caused by ephedrine alkaloids (the dose was not specified), the agency expressly relied upon the Dulfano and Tashkin studies cited by the Panel, as showing that the 25 mg dose level was safe. 51 Fed. Reg. 35326, 35331-31 (October 2, 1986).

[16] In addition, the agency had before it all the other scientific materials contained in the Ad Hoc Committee's 1500-page scientific submission to agency of July, 1995. We suggest that it was the distribution of this submission to the Working Group that may have contributed to its decision not to impose any unreasonable dosage limitation upon ephedra herb supplements.

clearly should have led to something other than blind acceptance of the inconsistent AER's.[17]

Fourth, the agency has created the appearance that there are many, and some serious, adverse events which it associates, however inaccurately, with ephedra herb dietary supplements. FDA's desire to make a "case" against ephedra (and DSHEA) has clearly gotten in the way of its best scientific judgment.

A case in point: testimony before the Working Group in October, 1995, showed that seven ephedra adverse events attributed to dietary supplements, distributed by Omnitrition, in fact involved products containing no ephedra at all (Testimony of Michael Betz, Esquire, in Ref. 27). These obviously erroneous AER's were identified by number, yet ten months later, all of them were included on the agency's list of AER's.[18]

In the same vein, the agency counted – and presumably integrated into its various tables in the Proposal – a substantial number of medically impossible AER's. These involve AER's claiming ephedra herb products caused a person to have conditions never associated with ephedrine in the medical literature: e.g., Lou Gehrig's disease, multiple sclerosis, excess hair, perforated colon, manic depression, "assaulted a woman," menstruation at age 76, pregnancy, hepatitis, a permanent erection, etc. AER's of this sort should have been ignored by FDA, as they would have been if they were allegations in a drug application. Instead, CFSAN counted them to support its preconceived intent to ban these products.

Likewise, the agency included in its "body count" a number of mild, expected responses, comparable to those seen in both the agency's OTC review and in clinical studies of ephedrine. Such AER's as "tremors," "abdominal pain, cramping and constipation," "itching," "nausea and perspiration," "skin rash," "increased energy, insomnia," "lack of concentration, inability to swallow," and the like – none of which are serious or life threatening, all of which self-correct upon continuation or cessation of exposure to the product and all of which were noted by the OTC panel when it found ephedrine safe – were included only to artificially increase FDA's AER total.

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[17] Aside from the scientific inconsistencies and medically impossible effects accepted by the agency, its submission to the record supporting the Proposal involved missing pages, deletions that sometimes obscured conclusions, etc. We agreed with the comments for Starlight that this Proposal should not be allowed to go forward on the state of the record, even as slightly amended, and an extension should be granted to correct and explain the record.

[18] When Mr. Betz of Omnitrition complained about the agency's failure to delete these AER's involving non-ephedra products, CFSAN's Dr. Lori Love commented that one individual might have consumed an ephedra product without realizing it (Ref. 25). This incident underscores the Center's desire to adopt a regulation effectively banning ephedra herb dietary supplements, whether the evidence for such action exists or "might" exist. Indeed, the Proposal covers "products [that] contained, or were thought to contain, a source of ephedrine alkaloids." 62 Fed. Reg. at 30679, emphasis added. As the Omitrition experience indicates, however, the agency will continue to believe a product contains ephedra (for AER purposes) even when the manufacturer shows it does not.

For the same reason, FDA included other AER's where the product expressly contains no ephedra (e.g., AER's 8787, 9299, 9329), or – in numerous cases – where the ingredients of the product involved are unknown (E.g., AER's 9489 through 9553). Even more commonly, the FDA lists adverse events supposedly caused by ephedra when the amount consumed is completely unknown, or in excess of labeled doses.[19]

FDA's most indefensible misuse of the AER's involves the reports of deaths, which it seeks to associate with ephedra herb supplements.[20] While blaming many of these reports on ephedra consumption is just plain silly – such as the AER's for the death of a store clerk who was shot, or the AER for a person who died in an automobile accident – the misuse of other deaths is medically indefensible.

An obvious case in point: ARMS No. 9864 (62 Fed. Reg. at 30719) was a 44 -year old male, who was found deal in his home. He had been taking an unidentified ephedra product for about three weeks before his death, and for that reason alone, FDA concludes that his death was caused by this supplement.

However, the autopsy report (which the agency has) shows that this conclusion is nonsense. It reveals that the deceased suffered from a pre-existing heart condition, arteriosclerotic plaque in his left descending coronary artery, producing a 50 percent blockage of the vessel. This is not a condition that could have been caused by consuming an ephedra herb dietary supplement, and certainly not in the three weeks he had been using the product. The partially occluded coronary artery was then completely blocked by a "soft pink thrombosis," again a condition not known to be caused by ephedrine.

The medical examiner concluded that the manner of death was "Natural." He explained: this individual "died as a result of acute coronary thrombosis. A blood clot formed in one of the coronary arteries in a region of atherosclerotic plaque . . . [He] died suddenly, consistent with a sudden cardiac arrhythmia due to the coronary occlusion." (Tab 4). Moreover, a toxicological screen done as part of the autopsy showed that there was no amines (including no ephedrine alkaloids) in his serum when he died, thereby excluding any possibility that the consumption of any ephedra herb dietary supplement was the cause of his death. (Tab 4) And, as noted, the medical examiner found his death was natural.

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[19] Expected responses are not usually counted by FDA as adverse events, especially when they are mild, not life threatening, and disappear with continuance/cessation of product use. Adverse events are those which are unexpected and severe.

[20] FDA seems unable even to quantify the number of deaths which it associates with products containing ephedrine alkaloids. On successive pages of the Proposal, the agency asserts there were either "multiple deaths" or, conversely, only "in a few cases, death" (Id. at 30678, 30679). It relies, however, on only six deaths, among the 53 AER's cited in the Proposed. As with the death discussed below, none of the other five deaths FDA tries to relate to ephedra can withstand careful scientific and medical analysis, the kind of careful analysis which FDA should have applied before issuing the Proposal. (Tab 2).

Finally, attributing death or any other adverse event is difficult, if not inappropriate, where there is no data with regard to the amount of the chemical consumed. Under the Dietary Supplement Health and Education Act of 1994, an herbal dietary supplement constitutes a "substantial or unreasonable risk," and thus is subject to FDA action, only where the risk exists when the product is consumed at labeled dosages. Yet FDA has dosage information, and that fragmented and not always reliable, for barely twenty percent (11/53, see Tab 2, Cover Letter) of the AER's it relies upon – in all the others, FDA does not know whether the individual exceeded the recommended dosages.

In some cases – such as AER 10862, a death – the admitted single dose consumption was at least twice the daily labeled amount. Toxicology results indicate that his individual surely took other products that may have caused or contributed to his death (Tab 3). In any event, this death represents a conceded abuse/overdose situation, so it provides no evidence that there is any risk from consumption consistent with the usual single dose (25 mg.) of ephedra herb dietary supplements. FDA should have deleted this case from the AER's it relies on.

Fifth, the Proposal cannot be adopted because FDA has failed to show that individuals who consume ephedra herb products are at any greater risk for serious (or other) injuries than those who do not. This comparison is basic to any determination that a chemical has a benefit when given to humans (OTC drugs, prescription drugs, biologics, etc.), or that it may be harmful (all of these plus food additives, and any food or cosmetic thought to cause harm). It is particularly important to reach such a determination where, as here, there is only limited, anecdotal data to contravene the extensive clinical literature on ephedrine alkaloids. Absent evidence from such a comparison, there is no basis for associating a serious injury with ephedra herb consumption, because there is no basis for excluding the possibility that the injury occurred by chance.

For example, it has been estimated that there are about 164,700 first unprovoked seizures per year (61 per 100,000, population of 270,000,000), two thirds of which have no clearly identified antecedent. Mayo Clinic Proceedings 71: 576-586, 1996 (Rochester Minnesota Area). This is an incident rate of about .040%. Thus, among the minimum of 20,000,000 Americans who consumed ephedra herb dietary supplements during the period FDA was soliciting AER's, we would expect there to be about 8,000 seizures for which there is no identified cause. Only a comparative handful of seizures were reported to FDA, and even accepting the agency's unlikely assumption that 90% of seizures go unreported, there still seem to be far fewer seizures associated with ephedra herb consumption, than are seen in the general population which does not consume these products.

Likewise, with strokes: in 1990, there were 392,334 first strokes. American Journal of Epidemiology: 144: 665-673 (1996). This is an incidence in the general population of 1.45% (392,344 divided by 270 million). Among the minimum number of individuals consuming ephedra herb product even in a single year, 5,000,000, we would expect a stroke incidence of orders of magnitude greater than what FDA has reported. So once again, the comparative handful of strokes among those who consume this herbal product appears to be fewer than would be

expected in the general population, and thus simply cannot prove a "cause and effect" relationship.

Plainly, the presence of a few unexplained seizures or strokes among those who consume ephedra herb products does not provide they are caused by these products, nor that consumption of these supplements increases the risk of having a seizure or stroke.

These examples also serves to illustrate the complete absence of any "denominator data" supporting the FDA's arguments that its 800 AER's are significant, or that they support this unreasonable Proposal. The AER's that have been reported – pursuant to significant encouragement by the State of Texas, FDA, and the press – over the past four years, come from a population of ephedra users best estimated at 20-32 million people; some 4.4 billion doses of ephedra herb supplements were sold during that time (excluding sales of "get high" products) (See testimony of Michael Ford, NNFA, Ref. 25). Thus, if all 800 of these reports were valid (and at least 90% are not supported), the incidence of injury from ephedra herb products would range from .004% to .002% of those who consume these supplements, far below most of the acceptable risks of life.

Even forgetting the necessary "dominator data," and meeting the Proposal on its raw numbers, it is clear that ephedra herb products, containing a small percentage of ephedrine alkaloids, are among the safest consumer products available. FDA's parent agency, the Department of Health and Human Services, compiles data on emergency room admissions caused by various OTC drugs, foods, and other chemicals. For two recent years, 1991 and 1992, ephedrine-containing products ranked 69th in causing emergency room admissions, far behind the admissions for many FDA approved OTC drugs (Tab 7). This HHS data, so at odds with the Proposal, can be summarized as follows:

Emergency Room Admissions

Product	Year	Number
Acetominophen	1991	30,883
	1992	31,355
Aspirin	1991	21,982
	1992	18,894
Ibuprofen	1991	13,628
	1992	16,894
OTC Sleep Aids	1991	6,434
	1992	7,034
Phenobarbital	1991	2,062
	1992	3,220

Caffeine	1991	2,287
	1992	2,397
Ephedrine	1991	955
	1992	902

(Data Summarized from Tab 7).[21] There were no reports of admissions based on ephedra herb supplements, since in 1991-1992 FDA and Texas were not yet soliciting such reports.

In sum, FDA's Proposal to strictly limit the labeling and use of ephedra herb dietary supplements – so that they will no longer commercially viable – does not represent the reasoned application of traditional and accepted scientific metrology: scientific literature review, review of animal studies, review of clinical studies, consideration of the regulatory status of the chemical, careful analysis of adverse events, and – most importantly – showing that those who consume the product thereby experience a result different from those who do not.

Instead of science, the agency relies upon literally a handful of anecdotal, adverse events, lacking adequate medical back-up in most cases, containing medically impossible conclusions in a substantial number, and failing to specify the amount consumed in more than 90% of the incidents (though the most widely publicized case concededly involved a deliberate overdose).[22] These anecdotal stories simply cannot overcome the substantial body of responsible scientific evidence and opinion – some of which is reflected in FDA's decision that 25 mg single doses (more than three times the level prohibited in the Proposal) ephedrine alkaloids are safe (21 C.F. Part 341) – showing that ephedrine alkaloids are safe for use at the customary single doses of up to 25 mg.

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[21] A private organization, Citizens for Health, surveyed the causes of death from FDA-regulated products over a ten-year period, 1983-1992. It found that there had been no deaths from herbal products, and only three deaths from all dietary supplements (caused by L-trytophan and iron poisonings); but there were 9000 deaths from food-borne illnesses, and over 90,000 deaths from prescription drugs (Tab 7). "Safe" OTC drugs caused more than 100 times the deaths associated with dietary supplements.

[22] FDA has repeatedly suggested that passive reporting systems underreport injuries. Since FDA, the Texas Department of Health and the press regularly urged the reporting of ephedra-related injuries, including numerous, widely-publicized press releases by the agencies, the reporting system here hardly seems passive. That aside, while passive systems may undercount less serious or obvious injuries, heart attacks, strokes, seizures, psychoses, and death will surely be reported. Given FDA's statements that these particular adverse events may be related to ephedra consumption, we suspect – and the AER's confirm – that these conditions were often reported when there was no causal link to ephedra. (E.g., one Texan related his problems to "read articles put out by FDA;" another reported "mild headaches and news releases" (Texas AR's 005692, 005683)).

II. There is Abundant Scientific Evidence Demonstrating that Single Doses of Ephedrine Alkaloids Up to 25 mg Are Safe.

FDA's Proposal does not reflect any effort by the agency to conduct a comprehensive study of the scientific literature on ephedrine in connection with its intention and efforts to regulate ephedra herb dietary supplements off the market. Nor did the agency even report the two clinical studies, by Dulfano and Tashkin – both showing that when 25 mg doses of ephedrine were given to healthy volunteers, they "had no significant effect on either heart rate or blood pressure," 48 Fed. Reg. at 38370. These are the studies on which its OTC Monograph's conclusion, that consuming 25 mg of ephedrine up to six times a day is safe, is based. Finally, when the Ad Hoc Committee provided two completely independent scientific literature reviews, by particularly well qualified experts the agency has relied upon, and attached to them over 200 articles from the scientific literature, the agency simply ignored them.[23]

A. Scientific Literature Reviews.

The Ad Hoc Committee commissioned, paid for, and presented to FDA, two separate and independent reviews of all the scientific literature on ephedrine and ephedra. The first was prepared by Dr. Dennis Jones, a Canadian scientist who is among the most knowledgeable individuals in the world on ephedrine and related compounds (Tab 8). The second was directed by Rob McCaleb, of the Herb Research Foundation, a member of the government's Commission on Dietary Supplement Labels, and written by Dr. Steven Dentali, a member of the FDA's Food Advisory Committee Working Group (Tab 11). These reviews exceeded 100 pages of text, and were accompanied by extensive bibliographies, including copies of about 200 of the most relevant articles.

(1) Dr. Jones set out the conclusions of the articles on ephedrine and ephedra as follows:

> Concerns have been expressed that . . . dietary supplements based on Ephedra herb (Ma huang), may represent health hazards to consumers . . . These concerns appear to be based on opinions that lack sufficient factual support . . . .
>
> [T]here have been more than 20 significant publications in prestigious scientific journals, describing the effects of ephedrine in doses of 60-150 mg per day for periods of up to 26 months . . . in over 500 subjects. [E]phedrine . . . did not cause increases in blood

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[23] FDA's list of References clearly does not constitute a review of all the literature. First, dozens and dozens of relevant articles are missing, including many of the ones expressly cited in our literature reviews. Second, many of the references are not to materials from the scientific literature. Third, the References are not used to come to conclusions, but rather to be inserted into the Preamble in order to support conclusions FDA has already reached.

> pressure or heart rate . . . There were no clinically important side effects in the reviewed studies . . . .
>
> Such effects as were seen . . . were transient and ceased rapidly ("tachyphylaxis") as subjects continued to use the treatments. . . . None of the above literature reports support the contention that ephedrine in reasonable dosage . . . would represent a hazard to health. To quote one of the authors . . . , there were "no side effects of clinical relevance." [Tab 8, p. 79].

Dr. Jones then summarized his review of approximately 150 of the most important articles from the scientific literature:

> Dietary Supplements containing genuine Ephedra herb (Ma huang), correctly formulated, are safe, provided that they are used in accordance with appropriate directions for use and with due observance of any cautionary statements on the label. [Tab 8, p. 3].

Dr. Jones reviewed in detail several dozen studies of ephedrine-caffeine combination products that were being tested for weight loss (Tab 8, pp. 14-27). Several of these studies involved single doses of 44-50 mg of ephedrine alkaloids, taken several times a day, plus varying amounts of caffeine (Tab 8, pp. 19, 21, 26). These were no serious side effects in any of these studies, including studies utilizing as much as twice the customary 25 mg single dose. Whatever minor effects were seen uniformly ended as the subjects continued to take, or discontinued, the product. These well-done, often peer-reviewed studies showed absolutely no hazard from ephedrine use, and thus confirmed the Dulfano (1973) and Taskin (1975) studies – relied on by FDA in the OTC ephedrine monograph but omitted from the References – which also showed no harm from 25 mg doses of ephedrine.

The absence of any serious side effects in these studies is significant, because the patients were monitored closely by the treating physicians, whom they typically saw on a weekly basis.[24] Among the studies cited by Dr. Jones, and provided to the FDA, but not cited in the proposal's

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[24] The agency has argued that these weight-loss studies are "effectiveness" tests, and therefore have no bearing on the product's safety 62 Fed. Reg. at 30689 . Yet FDA itself rests its proposal on purely anecdotal adverse event data, much of which has obvious medical omissions and shortcomings. The weight-loss studies all report side effects in detail, with physicians carefully watching their patients for any serious effect elated to the treatment. The results are consistent over dozens of studies and hundreds of patients, and have much greater scientific value than the anecdotal reports of injuries FDA relies on, each of which amounts of a one-person, non-blinded, uncontrolled trial, which obviously has no statistical predictive value.

list of References, are[25]:

- Malchow-Moeller (1981): Three daily doses of 40 mg ephedrine and 100 mg caffeine for 12 weeks, double blind conditions, 132 patients enrolled, 108 available for evaluation. No serious side effects at all; there were minor side effects in all groups, many transient; and "there was no increase in BP or pulse during the treatment, and no change in laboratory parameters was found."

- Roed (1980): Three daily doses of 40 mg ephedrine and 100 mg caffeine for twelve weeks, largely blinded, 143 patients available for evaluation. No serious side effects, a few typical ephedrine side effects seen, but withdrawals due to side effects were comparable in the ephedrine/caffeine and placebo groups.

- Krieger (1990): Three daily doses of 25 mg ephedrine the first four weeks, 50 mg ephedrine three times a day for the second four weeks, both with 150 mg caffeine, for eight weeks, double blinded, 24 patients available for evaluation. No serious side effects, minor side effects not different between ephedrine and placebo groups, and no differences between the groups in heart rate of blood pressure.

- Other studies reporting no or only mild side effects from consumption of ephedrine and caffeine, or ephedrine alone, include Pasquali (1985) (Noting that all mild side effects were well-tolerated and tended to disappear as treatment continued, so there were no side effects whatever in the ephedrine group by the third month); Pasquali (1987a) (No clinically important side effects); Astrup (1990a) (No significant difference in side effects seen between placebo and ephedrine group; caffeine group experienced significantly greater number of effects); Pasquali (1992) (No significant side effects of any kind seen); Astrup (1992a) (Mild side effects were transient, occurring mostly in caffeine group, and no different from placebo); Astrup (1992b) (All side effects were mild and transient, disappearing in 6-14 days of administrations; Toubro (1993) (No side effects reported); (1992b) (All side effects were mild and transient, disappearing reported); Gessler (1993) (Treatment well tolerated, no difference in side effects); Pasquali and Casamirri (1993) (Side effects of a minor nature appeared only at the 150 mg daily dose level, not at 75 mg; those appearing are minor and disappear with time); Astrup and Toubro (1993) (No more reports of side effects with ephedrine than placebo); and Buemann (1994) (No side effects seen in eight week study of 60 mg ephedrine plus caffeine).

These clinical studies, as well as the additional literature cited by Dr. Jones, clearly show that fairly substantial amounts of ephedrine caused no reported serious side effects, even when the patients were being closely monitored by physicians. The studies involved 454 patients treated

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[25] The complete citations can be found in Dr. Jones' literature review, Tab 8, pp. 81-93.

with ephedrine plus caffeine, and another 113 treated with caffeine alone. (Tab 8, Tables, pp. 35-41). Dr. Jones analyzed this data, and concluded:

- There were no adverse effects of a toxic or threatening nature. All side effects reported, most of which were subjective, could be explained on the basis of known pharmacological properties of the ephedrine or caffeine. These side effects were classified by the various authors cited as minor, transient, and lacking clinical relevance.

- Treatment with ephedrine, with or without caffeine, had no effect on blood pressure or heart rate. . . [therefore] some investigators felt entirely justified in treating patients with mild hypertension (diastolic blood pressure <110 mm Hg).

- The perception of typical ephedrine effects was generally very early in the course of treatment and transient (< 1 week). After the first month, the incidence of such side effects was often lower than in placebo groups.

- The incidence of typical ephedrine effects was much reduced or even zero if patients were allowed to acclimatize to a low initial dose of ephedrine (<75 mg/day) before moving to a higher dose.

(Tab 8, p. 44).[26]

Dr. Jones' conclusions were confirmed by Dr. Arne Astrup, recognized as the leading researcher and expert in this area. In a letter to Dr. Jones, Dr. Astrup wrote:

> I agree with you that there is no evidence that there is a risk in the use of ephedrine/caffeine, and our paper [Astrup (1992a)] actually shows that all cardiovascular risk factors develop beneficially during treatment with ephedrine/ caffeine.

(Tab 8, p. 44).

Clinical studies aside, there is a substantial body of scientific literature attesting to the safety of ephedrine and ephedrine/caffeine when used at moderate doses (i.e., 25 mg for up to four times per day, a level below that used in most of the reported clinical literature). E.g., Gahart (1985); Southon (1989); Dharmandra (1994); Battig (1993). Indeed, due to these articles showing ephedrine's safety at 25 mg single doses, virtually all of the more serious effects noted in the literature relate to the deliberate or accidental abuse of ephedrine at high doses.

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[26] In addition, Dr. Jones reported on six short-term studies, in which an additional 138 patients were exposed to single doses of ephedrine at 22-60 mg. No side effects of any sort were reported by the investigators (Tab 8, pp. 45-46).

Dr. Jones collected almost "all of the adverse events reported in the medical [literature] during last 30 years," involving ephedrine alkaloids, and summarized them as follows:

Dermatological: 1 (apparent moderate dose);

Neurological/psychiatric: 25 (all due to abuse);

Cardiovascular/stroke: 1 (apparent moderate dose)
1 (simultaneous with MAO inhibitor)
3 (due to abuse).

(Tab. 8, pp. 45-46).[27] Thus, the literature reports only two serious adverse events that do not involve abuse of ephedrine.[28]

Finally, while the literature shows that, absent abuse, customary single doses of 25 mg of ephedrine alkaloids are safe, it also supports the safety of ephedra herb supplements. There is a paper on the safety of the herb, Jones (1993), and the results of a larger formal clinical trial using the herb, rather than an ephedrine extract. Kaats & Adelman (1994). In the clinical study, with a double-blind, crossover design, 100 subjects received a herbal formulation containing Ma huang at an average dose of 23 mg, 5 doses per day (115 mg/day), for a period of 8 weeks. No side effects of any sort were reported by the authors, and specifically no changes in blood pressure were seen (Tab 8, p. 79).

In sum, viewed objectively, the scientific literature shows that ephedrine alkaloids are safe for use at single doses of 25 mg, or slightly more. Dr. Jones' review, and the articles that were

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[27] FDA's original Health Hazard Analysis relied in part upon Garriott (1993), "Five Cases of Fatal Overdoses from Caffeine-Containing 'Look-Alike' Drugs." (Tab 9, HHA, p. 14; Tab 8, Jones' Review, p. 55). Yet four of these deaths were deliberate, suicidal overdoses, and the fifth was either an intentional or an accidental overdose – so the paper is not supportive of any risk from consumption at labeled doses. Moreover, it illustrates Dr. Jones' point that serious injuries from ephedrine in the literature almost always involve substantial abuse.

[28] For example, the overdoses necessary to create a serious psychotic episode are substantial. Whitehouse & Duncan (1987) report two severe cases of paranoid psychosis. One was a 65-year old male who had been taking 1700 mg of ephedrine per day, and who had recently increased this dose. He was taken off ephedrine and discharged symptom-free. The second was a 54-year old female who had been taking 2250 mg of ephedrine per day for as long as 20 years. Removing her from these exaggerated doses of ephedrine resolved her symptoms. Loosmore & Armstrong (1990) report three similar cases, where the patients were taking, respectively, 660 mg for 15 years; 198-265 mg per day for 30 years; and 330-660 mg for 15 years. Significantly, "despite use . . . at doses up to 20 times the normal maximum daily dose, there was no evidence of permanent harm . . . and the symptoms resolved completely within a very short space of time" (Tab 8, pp. 53-54). The same thing is seen throughout the scientific literature: individuals taking massive doses of ephedrine for extended periods of time without suffering any permanent adverse effects. See Ref. 66 ("chronic excessive ephedrine intake" of 400 mg a day for 16 years); Ref. 67 (up to 450 mg day for 10 years); Ref. 68 ("heavy ephedrine abuser" taking 2000 mg daily).

attached to it, rebut any argument by FDA that the literature supports its Proposal.[29]

(2) Rob McCaleb, President of the Herb Research Foundation, among the country's leading experts on herb safety, and for that reason a member of the government's Commission on Dietary Supplement Labeling, was retained by the Ad Hoc commission to prepare a scientific literature review of ephedra. He hired Dr. Steven Dentali, a well-recognized expert on herb safety and a member of the FDA's Food Advisory Committee Working Group considering ephedra, to prepare the report, along with other experts in specific areas.

Dr. Dentali began by pointing out that consumption of ephedrine alkaloids from dietary supplements "is well within the [safe] limits" for OTC exposure (Tab 11, p.1). Moreover, long-time Chinese uses, ranged from 3-9 grams per day, "equivalent to as much as 75-225 mg per day of Ephedra alkaloids" (Tab 11, p. 4, citing Bensky (1986), Hsu (1986) and others). Apparently, even at these elevated doses, no adverse events were seen, and the users survived, a result often seen in the scientific literature.

Dr. Dentali points out that the "usual [safe] adult dose for administering ephedrine orally as a bronchodilator is 25-50 mg every 3 or 4 hours" (Tab 11, p. 11). Moreover, with continued use, a "tolerance (tachyphylaxis) [develops] to the CNS and pressor [blood pressure] effects of ephedrine" (Tab 11, p. 13). Thus, continued use over time does not suggest an increased risk of serious injury, but rather a reduction.

Moreover, while FDA has occasionally stated that ephedrine is related to amphetamines, its "subjective effects. . . more closely resembles caffeine" (Tab 11, p. 13, citing Chait (1994)). So, as shown in Bruno (1993), "findings do not suggest that the use of ephedrine according to manufacturer's recommendations is a risk for stroke" (Tab 11, p. 13, citing Bruno). Likewise, while the literature includes cases associating ephedrine consumption with a psychotic episode, "the daily dose prior to the psychotic episode . . . [was] an average of 510 mg" (Tab 11, p. 13, quoting from Whitehouse & Duncan (1987)).

Despite some of these exaggerated consumptions, "ephedrine is believed to be a stimulant with a relatively low liability for abuse" (Tab 11, p. 13). "Alkaloids isolated from Ephedra . . . have found their place as safe and effective . . . for various uses" (Tab 11, p. 14).

Dr. Dentali concludes his literatures review by stating:

> Compliance with industry guidelines should provide customers with products as safe or safer than non-Ephedra ephedrine containing

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[29] Dr. Jones quotes Bruen (1993), to the effect that in a Danish population exposed to an ephedrine/caffeine combination weight loss product, there were only 86 adverse reactions reported, none of them serious, from 9.6 million doses (Tab 8, p. 31). Likewise, Dr. Jones was involved in conducting a retrospective study in Canada involving 230,000 individuals who had consumed 60-120 mg of ephedrine in a typical ephedra herb supplement, for a minimum of 6 weeks and an average of 11 weeks. No serious side affects were reported from this retrospective study (Tab 10).

products available over the counter.

(Tab 11, p. 14). Thus, these two independent reviews of the scientific literature agree that ephedra herb products are safe at customary single doses of 25, three to four times per day.

The Proposal ignores this literature and seems to have overlooked these reviews, which were presented to the agency in July and October, 1995[30], and again in August, 1996. Their conclusions are simply not outweighed by the 53 anecdotal and often incomplete adverse event reports, only eleven of which have any consumption data, cited in the Proposal.

B. Original Animal Research.

(1) The drug ephedrine was studied extensively, in various appropriate animal species, by the Department of Health and Human Services (FDA's parent agency) as part of the National Toxicology Program (NTP). These 1986 studies used extremely high levels of ephedrine on a milligram to kilogram (mg/kg) basis, and also involved exaggerated dosing methods (intravenous or interpersonal injection), which increase the ephedrine's impact as compared to human oral dosage.

The NTP published its results of the extensive safety testing of ephedrine sulphate (ES; USP grade 1-ephedrine sulphate) in F344/N rats and B6C3F mice. The studies were performed at the request of the National Cancer Institute, and motivated by the widespread and long-term use of ephedrine for the relief of symptoms associated with asthma. In fact, the NTP report notes that not only have humans long been exposed to ephedrine, which occurs in a variety of plants, but that production levels of autonomic agents in the United States ran at 1.151 million lbs in 1983. This, together with the presence of ephedrine alkaloids in a variety of popular non-prescription products, serves both to emphasize ephedrine's widespread use, and to point to the insignificant number of AER's, in light of the extensive use over a long period of time.

Single dose range-finding studies in rats indicated median lethal doses (LD_{50}), after oral administration, of between 150 and 300 mg/kg of body weight in male rats, and between 75 and 150 mg/kg in female rats; this is lower than the 600 mg/kg previously reported, but the strain of rat may play a role. In mice, the LD_{50}[31] values found were 812 mg/kg in males and 1072 mg/kg in females.

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[30] The Ad Hoc Committee submitted its 1500-page scientific report (in two volumes) to FDA in July, 1995. When we arrived to testify at the Working Group meeting in October, 1995, we discovered the agency had withheld this material from the Working Group. We provided a copy to each member and, at the FDA clerk's insistence, another copy to the agency. We provided these materials to the agency again in August, 1996, in a slightly different format, and with additional supporting evidence.

[31] Expressed in terms of a 70 kg human, the LD_{50}'s for ephedrine were, at a minimum, 5250 mg/dose (rats), and 56,840 mg/dose (mice).

In 14-day feeding studies, rats were first given ephedrine at levels up to 1200 ppm in drinking water, but this reduced water consumption; however, the maximum dose still corresponded to a dose of about 90 mg/kg/day. No animals died during the administration period, and there were no compound-related effects found at autopsy. This 14-day study was repeated, giving ephedrine in the feed at levels up to 1500 ppm (= 120 mg/kg in females, 148 mg/kg in females). None of the rats died before the end of the 14-day period, and at autopsy there were no clear compound-related effects.

In subsequent 13-week studies, rats were given ephedrine via the feed at levels up to 2000 ppm (= 87 mg/kg in males, 144 mg/kg in females). Rats given the highest dose level were hyperexcitable and had rough coats. None of the rats died before the end of the study, and no compound-related histopathologic effects were seen.

Corresponding 14-day studies were performed in mice, but with ephedrine levels up to 5000 ppm of water (about 350-400 mg/kg) or feed (850-900 mg/kg). Except for 1 male and 1 female mouse in the feed study receiving 2500 ppm (not the highest level), all animals survived to the end of the administration period. No compound-related effects were seen at autopsy.

The same dose levels (maximum 5000 ppm, or about 665 mg/kg in males, 900 mg/kg in females) were used in the 13-week study. All females survived 13 weeks, but deaths occurred in male mice at ephedrine levels in feed of 1250, 2500 and 5000 ppm (2 of 10, 5 of 10 and 1 of 10 respectively). These deaths were due to fighting.

Clinically, rough coats, hyperexcitability, and fighting among males were compound-related. However, there were no compound-related histophathological effects seen at autopsy.

Since the reduced weight gain occurring with higher levels of ephedrine was thought to be potentially life-threatening over the duration of the 2-year study, dose levels of 125 and 250 ppm (of feed) were selected for his segment, corresponding to 4 mg and 9 mg/kg in male rats, 5 mg and 11 mg/kg in female rats, 14 mg and 29 mg/kg in male mice and 12 mg and 25 mg/kg in female mice.

Survival of ephedrine-treated female rates in the 2-year study was higher than that of controls at both dose levels (control, 27/50; low dose, 39/50; high dose, 39/50). Survivals of ephedrine-treated male rats, and both male and female mice, were comparable to controls. The incidence of neoplasms in the 2-year study was low, and unrelated to treatments given. As was expected, administration of ephedrine reduced body weight gain, and this could not be entirely accounted for by reduced feed intake, suggesting the obvious weight loss effects (termogenics) of ephedrine.

Under the conditions of these studies, there was no evidence of carcinogenicity in the animals used. In addition, ephedrine was shown to be devoid of mutagenic activity in three specific test systems.

In general, these findings confirm the low toxicity of ephedrine as well as the lack of carcinogenicity and mutagenicity, and are in keeping with conclusions by other experts (Dharmandra, 1984; Gahart, 1985; Southon and Buckingham, 1989; The American Spectrum Encyclopedia, 1991). In fact, at dose levels of 200 - 400 times the recommended maximum dosage in humans (150 mg/day or about 2 - 3 mg/kg body weight per day), ephedrine failed to give any indication of organ toxicity over a 13-week administration period, and the pharmacological effects likewise proved to be insignificant.

One summary of these studies concludes that the "minimum lethal dose by intravenous injection of rats, rabbits, cats, and dogs is 66-140 mg kg (equivalent to 4620-9800 mg or 185-392 [25 mg] tables for a 70 kg [154 lb.] human)." Further, in "the worst case situation in mice . . . he LD50 of ephedrine by intraperitoneal injection was 13.5-28 mg/kg body weight (equivalent to 945-1960 mg or 38-78 [25 mg] tablets for a 70 kg human)." In addition, "repeated doses of ephedrine showed no cumulative effects," and animals "given less-than-lethal doses recovered completely with no ill effects." Finally, dosing some of the animals at less than these highly exaggerated levels, i.e., "4-29 mg/kg body weight . . . equal to 280 to 2030 my day [.e., 11-83 25 mg tablets] for a 70 kg human," produced no significant effect on "2-year survival of mice or rats except as also noted by Dr. Jones, to <u>increase</u> survival of female rats" (Tab 12, emphasis in original).

(2) The Ad Hoc Committee complemented these results by commissioning original acute (24 hour) and subacute (14- and 21-day) safety feeding studies using a typical ephedra herb dietary supplement, in rats, mice and dogs. The acute study measured the impact of very high levels of ephedrine on the animals, while the subacute studies essentially repeat the acute studies (because ephedrine is rapidly excreted) over a longer period of time. According to the FDA "Redbook," these are the appropriate studies to measure the risk of a substance which, like ephedrine, has no long-term potential health risk. The animals studied, the rate, mouse and dog, are those likewise identified by FDA as appropriate for such testing.

The animals were given an ephedra herb product at 32.7, 163.5, and 327 mg/kg of body weight, which in a 154 pound person is the equivalent of a single dose of 2289, 11,445 mg, or 16,100 mg. In addition, the animals were fed by gavage, which involves tubing the entire dose directly into the stomach, thereby exaggerating the animal's response.

Two of the four dogs died, as would be expected in an LD_{50} study (i.e., the highest dose is intended to be a lethal dose for half the animals). However, the acute rat and mouse studies produced no deaths, and only a few transitory effects, at the highest level. Thus, a hazardous level could not be set for this ephedrine-caffeine combination.

The studies were reviewed by Wayne Snodgrass, M.D., Ph.D., then the chairman of the Poison Center Coordinating Committee for the State of Texas, and a medical specialist in acute responses to food ingredients and other substances. Dr. Snodgrass concluded that along with the scientific literature, the animal testing results showed that his typical ephedra herb product "does not pose any known unreasonable health risks to the general population in its availability as an herbal product" (Tab 12).

Dr. Snodgrass's conclusion was confirmed by Michael Scott, of Science Toxicology and Technology Associates, who directed and supervised the study. He concluded:

> Based upon the results of the laboratory study performed . . . , the scientific literature reviewed, the package warnings and labeling, and the research of ST&T associates, it is our conclusion that [the ephedra herb product] is safe when used as directed. [Tab 12].

(3) The Committee subsequently learned of another animal study which tested the effect of a commercial ephedra herb powder, rather than ephedrine, in mice. Law, Pedersen, Hennen, and McCausland, "Sub-Acute Toxicity Study of Ma-Huang in Mice" (Tab 12). This study indicated that ephedrine alkaloids may have a lower LD50 dose level than commercial ephedra herb products: half the animals died when consuming 300 mg/kg of ephedrine, but it required 4000 mg/kg to reach that result with ephedra herb powder. An even higher amount of the unextracted ephedra herb would be required to achieve an LD50 dose.[32]

The authors of this study concluded that "Ma-huang powder extract is safe up to a daily dose of 1000 mg" in male and female mice. This provides a safety level hundreds of times higher than either the safe FDA OTC amount (25 mg dose/150 mg day), or the level encountered in typical ephedra hereby products (20-25 mg dose/60-100 mg day). Thus, extensive animal testing of ephedrine and ephedra herb products shows them to be safe for humans.

C. Review of the Anecdotal Materials.

In the more than four years between the first AER reported (8475, March 29, 1993) and the date of the proposal (June 4, 1997), between 20,000,000 and 32,000,000 Americans consumed over 4,400,000,000 servings of ephedra hereby dietary supplements, according to the estimates of Dr. Dennis Jones and Michael Ford, executive director of the National Nutritional Foods Association (Ref. 25). During that period, and from that massive number of consumers, FDA has recorded some 800 adverse events, of which its proposal relies upon just 53 AER's, 42 of which have no data on the quantity consumed (Tab 2).[33] This is an incidence rate so small as to be almost unmeasurable: 53/26,000,000, or one alleged injury for abut every 1.3 million consumers, or .0002%.

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[32] This study supports other investigations reported in the scientific literature, which suggest that consuming the ephedrine alkaloids in an ephedra herb dietary supplement does not produce the same toxicological impact, even when the amount of ephedrine is the same on a weight basis. Ephedrine is present at six to eight percent in the herbal product, but at 100 percent in the drug; nothing buffers its effect in the drug.

[33] The agency has contended that ephedra herb products are subject to abuse. If that were so, it would seem likely that many users, who dose levels are unreported, may have taken amounts in excess of the labeled directions, so that their AER's are not relevant under DSHEA.

Nevertheless, completely ignoring the volumes of scientific literature[34], the established safety of ephedrine alkaloids under the OTC monograph, the safe dose of up to 50 mg dose/300 mg day provided in Goodman & Gilman, the governmental and non-governmental animal studies showing no toxicity, and the trenchant criticism of the AER's the agency has received, FDA has chosen to accept the anecdotal AER's as "proving" the hazard of ephedra herb. This attitude, "don't give me the scientific facts, give me absurd anecdotes," is indefensible, particularly since, in the FDA's AER data, there is rarely any medical connection between the AER's and ephedra consumption, (Tab 2). In all but a tiny handful of cases, there is no consumption data at all.

FDA has received substantial criticism of the AER's from well-respected scientists. This has included:

- Michael H. Davidson, M.D., who testified before the Food Advisory Committee after reviewing the listed AER's, and the backup materials for about one quarter of the total, from which he found 84 serious AER's. His review showed that only 2 of these allegations were "probably" related to ephedra consumption, and both involved a "toxic" level. Dr. Davidson concluded: "In summary, with the exception of two cases of toxic exposure to ephedrine, there appear to be only infrequent possible associations of ephedra-containing products with severe adverse events." (Ref. 25).

- Dr. Joseph Borzelleca, a 40-year faculty member at the Medical College of Virginia, a world-renowned toxicologist, and frequent FDA committee member, reviewed AER 10862 (Peter Schlendorft) in detail. He concluded that it was impossible to determine, on the material the FDA had, "that the cause of this death was the ingestion of some quantity of a product containing ephedrine" (Tab 3, Att. 2, p. 4).

- Dr. Borzella, aided by his MCV colleague Dr. Graham Patrick, reviewed all "800" plus Texas AER's; these provided the largest portion of FDA AER's, and the state and the agency worked closely together. The experts found it impossible "to establish a causal relationship between ingestion of these products and any serious adverse effect," so they "appear to the safe when used in accordance with the instructions and warnings on the label" (Tab 5, Item 2, p. 13). Further review of additional Texas cases, including those Texas cases in FDA records, led to the same conclusion (Tab 5, Item 1).[35]

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[34] The Proposal cites the literature only where FDA believes it may support its position, even where such support is a distortion of what is said in the literature. (See Refs. 66-68.)

[35] Texas had proposed a rule making ephedra herb dietary supplements into prescription drugs. This regulation was supposedly based upon a review of 800 AER's, both by the Texas Department of Health (TDH) and the Texas Medical Association. Under pressure from the Ad Hoc Committee, the TDH was forced in January, 1997, to release the actual reports which related to dietary supplements (Tab 6). The number was not 800 but rather 109, with only 15 reports in 1995, and 8 in 1996. When the Texas reports were reduced to about one-eighth of the number reported to FDA, the agency did not purge those [fn. cont.]

In addition, the Ad Hoc Committee criticized the Texas and FDA AER's in detail in its submission to the agency in August, 1996.[36]

[fn. cont.] Texas AER's which the state could not longer support. Thus, for example, AER 10929, involving Nature's Nutrition Formula One, remains in the FDA record, but it no longer appears on the Texas listing (See Tab 6). Other errors followed when Texas corrected its reports, but FDA did not follow. For example, AER 11060 is listed by FDA as a "death," with information provided by "TDH." But on the revised TDH list, this patient is not listed as dying (See Tab 6, p. 3 (2-16-96, 64F). Thus, the reliability of the AER's has been undermined by TDH's belatedly telling the truth about the limited number of its adverse reaction reports.

[36] The Texas Formula One AER's comprised more than one quarter (155/608=25.6%) of the "Clinical Summaries of Adverse Event Reports on Dietary Supplements that May Contain Ephedrine Alkaloids," presented by FDA to the Food Advisory Committee in August, 1996. Yet the significance of these reports have been criticized by the officials who gathered them, including Dr. Wayne Snodgrass, chairman of the Texas Poison prevention Centers. Another critic was Dr. Michael D. Ellis, Director of the Southeast Texas Poison Center for 24 years. In a deposition, he testified that there are safe levels for the Formula One product "if you don't have some pre-existing condition" excluded by the label. He defined those safe levels as follows:

> With a normal individual, 25 milligrams of ephedrine . . . is a safe and effective dose . . . . [Y]ou probably could take that on an every four- to six-hour basis.

Then, when asked about the Texas AER's for 1993-1995, whether "none . . . indicate . . . uses resulting in injury or illness to someone, right?," he replied, "I think we can state that, yeah." Likewise, he added, "you couldn't make that case [for the product presenting a harm to the public] with those [19]96" reports (A copy of relevant portions of the Deposition is included in Tab 16).

Thus, several of the scientists employed by the State of Texas to evaluate acute poisonings, but who are not under the control of the Texas Department of Health, have confirmed that the Texas AER's do not show that Formula One, a typical ephedra herb product, poses any risk of harm. Perhaps the reason for that is best stated by an expert witness retained by the State for its litigation against Formula One, who explained:

> some of the cases may have had predisposing factors such as silent ischemic heart disease or a prior seizure disorder. However, most appear to be unpredictable and indicative of excessive exposure instead of supersensitivity.

(Texas AR 001601).

This discussion of the Texas cases is important because they comprise more than one-quarter of the first 600 ARMS. If the Texas scientists who helped gather these reports believe that they do not suggest that a conventional ephedra herb product poses any risk, a conclusion seemingly confirmed on January 16, 1996, when the Texas Board of Health set aside the proposed TDH regulation of ephedra, then there is no basis for FDA's using these AER's to allegedly show these products pose a risk. It also reduces the number of the agency's adverse events by 20+ percent.

These criticisms have been ignored, and based upon these 53 cases – containing some of the least defensible AER's that FDA has received – the agency rests its Proposal. We have had each of these AER's reviewed by Dr. Graham Patrick, a professor at the Medical College of Virginia and Dr. Joseph Borzelleca's partner in the consulting group, Toxicology and Applied Pharmacology. He has reviewed all the medical, consumption, and other evidence available to FDA, and has rendered his expert judgment in each case.

(1) Deaths Allegedly Caused by Ephedra Herb Products. Death is obviously the most serious adverse event possible, but it is almost impossible to believe the agency seriously believes that any of these six deaths in the Proposal were caused by consuming an ephedra herb dietary supplement. Chemical analysis of four of these individuals showed no ephedrine in the serum shortly after death; this makes it impossible for ephedrine to have caused the death. Three of the autopsy reports show "Natural" as the cause of death. And, we wonder whether the agency is serious in claiming that one individual with no ephedrine in his system, who died an in automobile accident, can fairly be described as a death caused by ephedra herb consumption? These is simply no relationship shown medically between ephedrine ingestion and the deaths in these six cases.

(a) Arms 11441. Dr. Patrick's analysis:

> This 27 year-old male used Ripped Fuel, two tablets twice daily as directed on label, for three years. He died secondary to injuries sustained in a motor vehicle accident. No autopsy was performed. Toxicology report included blood alcohol 0.05% and phentermine 0.31 mg/L, and urine positive for phentermine and negative for cocaine, opiates, benzodiazepines, and cannabinoids.
>
> No further records or documentation were available. No further information is needed to conclude that ephedrine was not a contributing factor in this death. No ephedrine was detected in the blood or urine, while ethanol and phentermine (a prescription stimulant) were. The immediate cause of death was traumatic injury sustained in the accident. [Dr. Patrick's analyses of all 53 ARM's are at Tab 2]

(b) ARMS 9864.

This 44 -year old male died after playing tennis. The medical examiner reported that the cause of death was a thrombis, blocking a diseased coronary artery, neither of which conditions are caused by ephedrine ingestion. The toxicology screen was negative for any ephedrine in his body. Thus, the medical examiner's conclusion that he died a natural death is obviously correct. [See more extensive analysis in Tab 4]:

Dr. Patrick's analysis:

> This 44 year-old male used Formula One as directed. Three weeks after starting product, after playing tennis, he was found dead. Autopsy revealed an acute thrombus, 1.5 cm from the origin of the left anterior descending coronary artery, resulting in occulsion. A drug screen performed at the time of autopsy was negative for amines.
>
> Thrombus formation is not an effect of ephedrine alkaloids. This thrombus occluding the left anterior descending coronary artery led to cardiac arrhythmia and myocardial infarction, the cause of death (according to autopsy report from another source.) The manner of death was indicated to be natural. Ephedrine alkaloids were not implicated in this death.

(c) ARMS 11134. This individual died after taking a product which, according to the FDA's analysis (Ref. 149a, Table), contained no detectable amount of ephedrine, but rather pseudoephedrine in modest amounts. His autopsy revealed no ephedrine in his serum, though a subsequent test of his urine for ephedrine alone (and no other substances) was positive. He displayed no evidence of any symptoms of ephedrine ingestion over the two year period. He died of "patchy myocardial necrosis," which had developed in the last week before his death (he had been consuming the product for two years). As Dr. Patrick notes, there is not a single case anywhere in the literature of ephedrine causing such a condition.

Dr. Patrick's detailed analysis (Tab 2):

> A 23 year-old male consumed multiple dietary supplements, including Ripped Fuel containing ephedrine alkaloids, for approximately two years. He was found dead in his apartment by his stepsister. There was no significant medical history nor evidence of trauma or substance abuse. Autopsy revealed "patchy myocardial necrosis" and "focal subacute myocarditis without fibrosis, with leukocytosis and eosinophilia consistent with chronic catecholamine use."
>
> In spite of the wording in the medical examiner's report concerning cardiac damage with "chronic catecholamine use," there is little or nothing in the medical literature to support such an association with ephedrine alkaloids (which are phenethylamines, but not catecholamines). For example, the three cases involving ephedrine which are reported in the literature and are referred to in the FDA Proposed Rule (References 66-68) all involved doses of ephedrine several hundred to more than 1000 mg per day for periods of eight to ten years. Those doses are at least an order of magnitude higher

than in this case, and the periods of exposure were several times as long. Further, the nature of the myocardial damage in the other cases was a slowly progressive congestive heart failure, from which both subjects recovered after discontinuing use of ephedrine. There are no other reports of death due to "patchy myocardial necrosis." Therefore, the earlier reports referred to in the FDA Proposed Rule are neither qualitatively nor quantitatively similar to this case and do not provide a basis for considering the cardiac damage in this case to be ephedrine-related.

With regard to the usage of ephedrine alkaloids in this case, the use data from the FDA Proposed Rule Ref 149a Table indicate that the product consumed by the decedent contained no detectable ephedrine and 14.8 mg pseudoephedrine per serving (one-fourth the maximum FDA-approved over-the-counter dose of pseudoephedrine). The initial toxicology test, which was described in the ARMS report as being negative for all other drugs, showed "nothing significant detected" for organic bases (including ephedrine) as well. Ephedrine alkaloids were only detected in the urine when a second, more sensitive toxicology test was performed at the request of an FDA investigator. More sensitive tests were not performed to attempt to detect any other drugs.

With regard to the condition of the subject, the autopsy report estimates the "patchy myocardial necrosis" lesions as being one week old. In agreement with that estimate, the decedent's stepsister and a friend described him as being very tired in the week before his death. They did not describe him as displaying any symptoms that would typically be associated with effects of ephedrine alkaloids, even when the investigator asked specifically about such symptoms. These observations suggest that there was some unidentified event or contributing factor that affected the subject approximately one week prior to his death. Although the medical examiner's report does mention the use of ephedrine alkaloids, it also has the box marked "Natural causes" checked as the manner of death.

In summary, there is nothing about the nature of this death that can be directly related to the consumption of ephedrine alkaloids. In fact, if the rather modest consumption of the alkaloids seen in this case could actually precipitate such damage, there should be numerous similar cases with clinical documentation. The fact there is not an abundance of such cases is prima facia evidence that ephedrine is not the cause in this case.

(d) ARMS 11248. The medical examiner concluded that this death was natural. Dr. Patrick explains (Tab 2):

> A 37 year-old male had used ephedrine products for approximately two years, and at the time of his death was consuming Formula One, one or two capsules midmorning and P.M. He died from sudden cardiac arrest, with no details of his death known. Autopsy noted cardiomegaly, left ventricular thickening, focal interstitial fibrosis and mild medial hypertrophy, as well as pulmonary congestion. Toxicology screening noted pseudoephedrine and caffeine in the urine.
>
> There is nothing to suggest direct involvement of ephedrine in this death. The exposure to ephedrine was stable over a two-year period without previous ill effects, and ephedrine was not detected in the toxicology testing. The subject was reported to have had a cold at the time of his death, and Congestaid (containing 30 mg pseudoephedrine per dose unit) was found in his first aid kit. This is a more likely source than Formula One for the pseudoephedrine found in the urine, especially since no ephedrine was detected. The subject was also reported to consume approximately 48 ounces of diet cola per day, a likely source of the caffeine detected.
>
> The cardiac abnormalities described in the autopsy report are conditions that develop over a long period of time, and they are not effects that would be attributable to exposure to ephedrine alkaloids. The pulmonary congestion was likely a result of the cardiac pathology and also a likely contributor to the acute cardiac arrest.
>
> The medical examiner's report stated that "death is, in my opinion, natural." That opinion is consistent with the available data and medical findings.

(e) ARMS 114217. This woman died of primary pulmonary hypertension. While this is a known adverse effect caused by FDA-approved weight loss products (Phen-Fen), there is absolutely no indication in the literature that PPH results from ephedrine ingestion. Moreover, there is no confirmation the deceased used any ephedrine-containing product, nor the amount she may have consumed, if any. Dr. Patrick's analysis (Tab 2):

> This 34 year-old woman died following diagnosis of primary pulmonary hypertension (PPH). Bottles of Thermojetics Herbal Tablets- Green and Beige were found in her home. Quantity and duration of use are unknown. The deceased appeared to be in excellent health until approximately three months prior to her death

> when she developed shortness of breath while skiing in Colorado. She was diagnosed with "high altitude sickness." Symptoms persisted and she underwent cardiac catheterization, with the results consistent with PPH. She died shortly thereafter. Medical history was significant only for hospital admission one year prior to death for chest pain, shortness of breath, and possible pneumonia.
>
> There is not sufficient information or documentation concerning use and medical records to permit a complete evaluation.
>
> It has been recently recognized, but now well recognized, that long-term use of some appetite suppressant agents leads to development of primary pulmonary hypertension. The risk of this usually fatal outcome increases with continuous use beyond three months. It has been observed most frequently with the serotonergic anorexiants such as dexfenfluramine, but has also occurred with adrenergic appetite suppressants such as phentermine. To my knowledge, cases of PPH have not been described with use of ephedrine alkaloids. Considering the widespread extent of their use for weight control (especially phenylpropanolamine) and their lesser efficacy compared with the agents mentioned earlier, it would seem that the risk of PPH with ephedrine alkaloids is minimal or perhaps nonexistent, but the possibility cannot be completely ruled out at this time.
>
> In this case, the chronic use of other, prescription appetite suppressants seems the most likely cause of PPH, unless it is known with certainty that the decedent took no products for weight control other than those identified in the report. If no other such products were used by the decedent, the Thermajetics products would be considered a possible contributing factor. The symptoms associated with the hospitalization one year prior to death were probably due to the emerging PPH.

(f) ARMS 10862. The death involved a 20-year-old male, who died during "party week" in Florida after consuming, among other substances, an overdose of Ultimate Xphoria, an illicit drug substitute product which has been the subject of numerous FDA Warning Letters. Thorough review of the evidence by three extraordinarily competent experts shows that this death was not the result of consuming Ephedra.

(1) Dr. Joseph Borzelleca, one of the country's leading toxicologists, reviewed the autopsy report, in which death was attributed by the medical examiner to "Cardiac Arrhythmia due to Synergistic Effect of Ephedrine, Pseudoephedrine, Phenylpropanolamine and Caffeine" (Tab 3). As Dr. Borzelleca explained, his review led him to conclude:

> I do not believe that the conclusions of the medical examiner [as to]...the cause of death,...cardiac arrhythmia due to the effect of ephedrine, pseudoephedrine (PPA) and caffeine, ...is supported by the material in the Report of Autopsy. [Tab 3]

In other words, Dr. Borzelleca found no relationship between the one-page summary conclusion (which does not cite nor refer to any particular medical and/or toxicology findings), and the physical and toxicological evidence obtained from the autopsy and subsequent testing done on this individual's body.

a. First, Dr. Borzelleca explained, the physical cause of death, cardiac arrest resulting from an arrhythmia "is not supported by the physical findings...The Medical Examiner reported no diagnostic abnormalities in the myocardium, implying the heart was normal." [Tab 3].

b. Second, Dr. Borzelleca pointed out that the toxicology and biochemical screens, the only ones listed in the Autopsy Report[37] were limited to "substances that the medical examiner had concluded were part of the tablets he ingested." He explained:

> A proper toxicological study would have looked for the substances which alone or in combination might have contributed to the death. There was a need to do histopathology and more toxicological analysis. This is particularly important because the vast majority of the gross pathological findings do not suggest a cause for the death. In such circumstances, it is particularly important to do a complete screen for any chemicals in the body fluids and select tissues. It is an all-too-common assumption that because someone was exposed to a certain substance, that substance must have been the cause of his death, and thus to do no further search for other agents or cause. [Tab 3]

c. Third, while reviewing the toxicology and biochemical screens, Dr. Borzelleca observed that the amount of ephedrine found in the body was clearly insufficient to have killed a young man like the deceased. He explained:

> the levels of ephedrine reported in the Report of Autopsy appear to be consistent with the survival for a generally health 20-year-old male. The pathology report does not suggest that he suffered from any condition for which the ingestion of ephedrine is contra-indicated...[Tab 3].

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[37] The report of Autopsy lists the toxicological and biochemical studies conducted, and makes absolutely no reference to, or mention of, any additional toxicological studies. Subsequently, in August, 1996, FDA asserted that there were additional toxicological reports from the autopsy, but refused to produce them in their entirety. These additional materials were obtained elsewhere in June, 1997, when they were reviewed by Dr. Borzelleca's partner, Dr. Graham Patrick (See discussion below).

For all these reasons, Dr. Borzelleca, an experienced and internationally known toxicologist, and frequent consultant on toxicology and pharmacology to the FDA and other government agencies, reached the judgment that "the conclusion of the medical examiner" (that ingestion of ephedrine and other substances caused Mr. Schlendorf's death) is not "supported by the material in the Report of Autopsy" (Tab 3).

(2) At the FDA Food Advisory Committee meeting in August, 1996, Dr. Dennis Jones, a Canadian scientist with extensive experience with ephedrine, and who authored one of the AHC's literature reviews of ephedrine, supplemented Dr. Borzelleca's conclusions with additional observations. He pointed out in the written submission of his company, Fytoresearch, Inc., that the biochemistry results in the Report of Autopsy showed "somewhat higher levels of ephedrine than could be accounted for by the amount of ephedra product taken"; "little caffeine (whereas the product was quite rich in caffeine)"; and "fairly large amounts of phenylpropanolamine (PPA)" when there are "negligible amounts, as norephedrine, present in the product." In this later regard, the PPA was "found in blood at more than twice therapeutic levels..." Dr. Jones concluded that

> Such results could indicate that he had not even taken the Ephedra product implicated, or that he had taken significant amounts of a product containing PPA at the same time.

(Tab 3, Jones, p. 1).

(3) Dr. Graham Patrick obtained a subsequent toxicology report on the deceased (CFSAN's Dr. Fred Shank had refused to make this report available, except in a version so expurgated that even the name of the person whose serum and urine was tested was expunged). Dr. Patrick reviewed this report in light of the autopsy and other materials (all quotations are in Tab 3). He noted, first, that the plasma concentration of ephedrine was equivalent to having consumed 10 25 mg tablets, or in other words, an overdose ten time the single does for most ephedra herb products. But he added: "Nevertheless, this excessive dosage should not cause death in a healthy young person," and "[t]here is no known lethal plasma concentration of ephedrine, because no deaths due to ephedrine along have been reported in the literature." [38]

Dr. Patrick also found, as had Dr. Jones, far too much PPA in the deceased's serum to be accounted for by the product consumption, and far too little caffeine. These results "suggest that something else, and possibly a PPA product, were consumed." Dr. Patrick concluded that the cause of death, cardiac arrhythmia, was not supported by any physical evidence; the level of ephedrine and alkaloids were far too low to have killed him; and "it cannot be concluded with any

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[38] Dr. Patrick had also reviewed all the AER's collected by the Texas Department of Health, including reports of intentional overdoses of products containing ephedrine (both as a drug and as a dietary supplement). He noted: "[I]n the record of the Texas Department of Health there were a number of cases of intentional overdose with ephedrine, in doses from 50 to 100 tablets of 25 mg each (more than 5 to 10 times the apparent ingestion in the present case), without any serious health consequence" (Tab 3).

degree of scientific certainty that he ingestion of ephedrine alkaloids was a precipitating factor" of his death (Tab 3).

(5) Dr. Patrick again reviewed these materials, plus the materials in the Proposal's record. His assessment of this death remained the same: there is no evidence that ephedrine ingestion was the probable cause of death (Tab 2):

> A 20-year-old male consumed Ultimate Xphoria, eight tablets at one time (double the directed dosage and double the maximum labeled consumption for 24 hours.) Approximately thirty minutes after consumption, the subject complained of being hot, sweating, and having a headache. Friends found him dead approximately eight hours later. There was no significant prior medical history.
>
> The autopsy report found no microscopic "diagnostic abnormalities" of the heart, but did note that the heart was "distended." The toxicology report noted that the decedent's blood contained ephedrine 920 mg/ml, pseudoephedrine 150 mg/ml, phenylpropanolamine (PPA, norephendrine) 360 mg/ml, and caffeine 1.5 mc/ml. The medical examiner attributed the cause and nature of the death to "cardiac arrhythmia due to synergistic effect of ephedrine, pseudoephedrine, phenylpropanolamine and caffeine, Accident (self-ingestion)."
>
> Cannabis was found in the room, on the decedent's chest and near his body, but the toxicology testing was negative for cannabinoids. Thus, cannabis is unlikely to be a contributing factor in his death.
>
> There are several facts to be considered relative to the reported consumption, the toxicology report, and the conclusion as to cause of death.
>
> With regard to the consumption, the reported blood level of ephedrine is consistent with the described consumption; i.e. the batch records of the manufacturer (not available in the FDA Record) indicate that the ingested dose of ephedrine approximated 200 mg. and a blood level of 920 mg/ml is commensurate with that dosage. However, the blood level of PPA (360) mg/ml) is much higher than would be anticipated, corresponding to an acute ingestion of approximately 100-150 mg. Neither native PPA in the product nor conversion of ephedrine to PPA in the body should produce a level that high. On the other hand, the blood level of caffeine (1.5 mcg/ml) is too low for the described ingestion. Batch records indicate that the approximate does of caffeine consumed

was 250-300 mg caffeine, while the measured blood level would correspond to a dose of 100 mg or less. These observations cast some doubt on the accuracy and completeness of the report concerning consumption. (The data above taken from the Supplemental Toxicology Report in this case, prepared by the National Medical Services, Inc., but not included in the FDA Record made available for review.)

With regard to the conclusion that a synergistic effect of the four drugs detected led to a fatal cardiac arrhythmia, the following quantitative data (obtained from the Supplemental Toxicology Report) should be considered. The blood level of PPA (360 mg/ml) was less than one percent of that reported in a fatal case of PPA overdose (48,000 mg/ml). The blood level of pseydoephedrine (150 mg/ml) was less than one percent of that reported in a fatal case of pseudoephedrine overdose (19,000 mg/ml). The blood level of caffeine (1.5 mcg/ml) was 0.5-2.0 percent (less than 1 percent of the average) of those reported in caffeine-related fatalities (79 to 344 mcg/ml, with an average of 183 mcg/ml). There is no reported fatal blood level for ephedrine itself, which could be interpreted as indicating that fatal overdose with ephedrine is less likely than for the other three drugs present. The combination of four "one percent lethal" dosages could hardly be viewed as likely to product an additive lethal effect. In fact, it is highly unlikely that this combination would produce lethality in healthy adults. The conclusion of the medical examiner as to cause of death is one of exclusion. This is, finding no other apparent cause, the cause was attributed to something that was detected.

Also related to the autopsy report, the medical examiner did detect that the heart was distended. Enlargement of the heart is usually a chronic process associated with some type of cardiac dysfunction. Such a dysfunction, if it did exit and went undetected, could contribute to a greater sensitivity of the heart to cardiac stimulant drugs and to the development of an arrhythmia.

Finally, the friend who found the subject's body reported (in a police report not included in the FDA Record) that the subject's head was entirely within a waste basket lined with a plastic bag. The potential role of asphyxiation or oxygen deprivation was never addressed directly, but that seems possible as a contributing factor.

In summary, it is apparent that the subject intentionally consumed an amount of ephedrine-containing product in excess of the maximum recommended. It is also apparent that the nature and

> time course of the acute effects described (health, sweating, headache 30 minutes after ingestion) are consistent with the reported ingestion and are probably attributable to he ingestion, although it is not clear that the ingestion was exactly as described. It is also clear that the blood levels of ephedrine alkaloids and caffeine detected in this case would not be deemed sufficient to cause death in a healthy young adult. However, those blood levels might be sufficient to precipitate an arrhythmia in someone with a cardiac abnormality or with exquisite sensitivity to ephedrine alkaloids for other unidentified reasons.

Of course, regardless of any disagreement over the cause of death, the undisputed fact is that the deceased consumed 8 to 10 times the standard dose for ephedra herb dietary supplements. He allegedly did so with a product, Ultimate Xphoria, which is an illicit drug substitute and a misbranded food subject to enforcement action from the Food and Drug Administration. There is no need for any new regulation to eliminate this illegal product from the marketplace, and it provides no basis for preventing the sale of other low-dose, safe ephedra herb dietary supplements because of the deceased's death, which seems unrelated to ephedra consumption alone.

In sum, the anecdotal reports of six deaths from a population consuming over 4,400,000,000 doses in the 1993-1997 period, provide no basis for concluding that ephedra herb dietary supplements, at commercial dosages and with appropriate labeling, pose any threat to health.

(2) Strokes Allegedly Caused by Ephedra Herb Products. Among the 53 AER's included in the Proposal, only two involve individuals who suffered strokes, which the agency obviously believes were caused by ephedra herb ingestion. These results are anamolies: some 20-32 million people consumed ephedra supplements during the period of time when these two strokes were reported. It seems likely that more people consuming ephedrine were struck by lightening than experienced a stroke. Moreover, the medical records do not support a causative effect for ephedrine in either case: in one, the physician correctly described the event as being "of questionable etiology;" in the other, the patient had stopped taking an ephedra product seven weeks before the stroke (her body had thus been free of ephedrine for some six weeks, regardless of her dose).

(a) ARMS 11105. Dr. Patrick found the probability that ephedrine contributed to this stroke "remote." His analysis:

> This 31-year-old female used the product Trim Easy for approximately one year for weight loss. She consumed two capsules three times daily for one month, then three capsules three times daily (the maximum recommended dosage) for three months, then six capsules all at one time once a day for eight months. She experienced "major weight loss" during the year, according to a friend. She developed dizzy spells which increased to twice daily

over a one-month period. She then suffered a stroke due to intracerebral hemorrhage with left hemiparesis and aphasia. CT and MRI confirmed the hemorrhage. Cerebral angiogram did not show any additional abnormality such an arteriovenous malformation. The subject smoked only four or five cigarettes per day.

The time course of usage of the Trim Easy is not stated precisely, so the relationship of usage to the adverse event is difficult to judge. The stroke occurred on the evening of 8/30/95, and the subject made purchases on the product in 7/95 and 8/95, so it should probably be assumed that she was using the product up to the time of the stroke. Also, there is no information concerning quantitation of ephedrine alkaloids in the product, so the dosage cannot be estimated with any degree of confidence. The young women was clearly taking larger single doses than the distributor intended, but apparently had done so for approximately eight months without prior complaints. That observation is probably the strongest argument against the implication of ephedrine in this case. That is, the subject was on a continuing and unchanging regimen of consumption for eight months without significant adverse effect, so continuation of that same dosage would not be expected to cause a sudden and severe effect. In addition, the fact that the dizzy spells had begun one month prior to the stroke and had progressively (if slowly) increased over that period suggests that some other process was ongoing during that month, and that an unidentified process was the precipitating factor in the stroke.

Finally, the probable mechanism by which a sympathomimetic agent such as ephedrine would precipitate a cerebral hemorrhage would be by causing a marked hypertensive episode. When the subject was admitted to the hospital following the hemorrhage, her blood pressure was 143/68 mm Hg, a pressure unlikely to be sufficient to initiate a bleeding episode, although her blood pressure at the time of the hemorrhage may have been either higher or lower.

The diagnosis in this case was "spontaneous intracerebral hemorrhage, of questionable etiology, with left hemiparesis and aphasia." The possibility that ephedrine was directly involved in this serious adverse effect cannot be excluded, but the probability seems remote.

(b) ARMS 11106. There is no possibility that ephedrine could cause a stroke in anyone seven weeks after they discontinue using it. As Dr. Patrick explains:

> the Fall. She has been diagnosed with panic attacks and depression and is undergoing psychiatric treatment. She has also been diagnosed with a "weak heart valve."
>
> There is no documentation of use nor medical records available, so a complete evaluation cannot be made. The early subjective effects of "weird" feelings and the first night of insomnia are quite likely due to the ingestion of ephedrine. After 24 hours post ingestion, there would be insufficient ephedrine remaining in the body to contribute to the more prolonged insomnia or to the psychological problems described. High doses of ephedrine may cause acute psychosis and chronic use of relatively high dosage may lead to paranoid delusions, but panic attacks and depression are not sequelae of acute (or chronic) exposure to ephedrine. The conditions encountered in this subject are undoubtedly idiopathic psychologic disorders. Acute ephedrine would not contribute in any way to a "weak heart valve."

(4) Cardiac Conditions Allegedly Caused by Ephedra Herb Products. There are five instances of various cardiac conditions which the agency relates to ephedra herb consumption, among the 20-32 million Americans who consumed these products during the relevant time period when these reports were received. All five of the patients survived. In the first of these, Dr. Patrick found that "it is highly unlikely that the ephedrine product was a factor in causing this adverse event" (Tab 2, AER 9316). In the other four, there was too little information in the administrative record to reach any evaluation. For example, in AER 9552, the patient was to have follow-up with a stress test, which if it indicated a cardiac abnormality, would tend to confer that the abnormality was the cause of her myocardial infarction. Likewise, in AER 9818, the treating physician notes that "if condition triggered by the ephedrine it would have worn off by now."[40] Finally, in AER 10275, the patient was a 63-year old smoker with chronic obstructive pulmonary disease, a much more likely cause of the ventricular fibrillation. She should not have been taking any product containing ephedra with that condition, and that is true as well for AER 9818, who had repeated angina attacks. Dr. Patrick's analysis:

(a) ARMS No. 9316.

> A 23 year-old female, who had used E'OLA AMP II Pro Drops the night before, was hospitalized with cardiac arrest. She underwent CPR, then was taken to ICE. She was diagnosed with "inferolateral myocardial infarction." Angiography revealed "lacerated coronary

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[40] Once again (see Footnote 39), the agency appears to be deliberately misquoting from a physician's medical comments, omitting that portion of a statement supportive of the safety of ephedra herb products, in the Proposal. The material quoted (62 Fed. Reg. at 30719) was: "new onset atrial fibrillation, possibly due to the stimulant effect of his dietary supplement;" the material omitted changes the meaning entirely: "if condition triggered by the ephedrine it would have worn off by now" (Tab 2, AER 9818).

(partial dissection) and hematoma at bifurcation of circumflex artery." She was also reported to be using other "diet pills," but dosage and duration of use were unknown. Her drug screen was negative. She was reported to be "doing well off product."

It is highly unlikely that the ephedrine product was a factor in causing this adverse event. The MI resulted from a hematoma (clot) at the bifurcation of the circumflex artery. Ephedrine alkaloids do not promote intravascular clot formation. Presumably an acute, severe hypertensive episode could lead to such an event, but the dosage in this case (estimated to be 15-20 mg ephedrine in 3-4 drops of solution) was far too low to cause such an episode. In addition, the time course of events argues against the involvement of ephedrine. Although precise times are unclear, the ephedrine was consumed the night before the MI, so the peak effect of the ephedrine would have occurred several hours before the adverse event. The potential role of the other unidentified "diet pills" is similarly unclear. It is doubtful that this event can be attributed to any exogenous factor.

(b) ARMS No. 9552.

A 35 year-old woman in good health, with no risk factors for CAD, used Formula One, one or two capsules twice daily, for thirty days. She stopped use for one week, then resumed at three capsules per day. Approximately six weeks later, she developed acute onset of throbbing, anterior chest pain at rest, pain radiating to left shoulder, numbness of left arm and hand, diaphoresis, and shortness of breath. When pain persisted, she was taken to the hospital. Pain decreased with sublingual nitroglycerin and was relieved with morphine plus nitroglycerin. Extensive tests led to a diagnosis of "acute non-Q wave MI probably secondary to coronary spasm." Angiogram revealed normal coronary arteries. She was discharged after four days on Cardizem, aspirin, nitroglycerin when needed, and was to have follow-up for a limited stress test.

There is insufficient information to make an evaluation. If the stress test showed any cardiac abnormality, or if she has exhibited symptoms since the reported episode, that would argue against a causal effect of ephedrine. In the absence of such information, it is possible that the ephedrine contributed to the serious adverse reaction, because ephedrine alkaloids have been reported to cause coronary vasospasm in some extremely sensitive individuals. On the other hand, if ephedrine was the proximate cause of the

reaction, it should have occurred prior to seven weeks of continuing daily exposure.

(c) ARMS No. 9818.

A 43 year-old male used Power Trim (no details of usage given) for six weeks, during which time he lost thirty pounds. He developed insomnia and atrial fibrillation. He was given Lanoxin for the arrhythmia. The next day he developed lightheadedness and entered the hospital. Extensive cardiac testing led to a diagnosis of "new onset atrial fibrillation, possibly due to stimulant effect of dietary supplement." He was treated with Lanoxin, Betapace, Verapamil, and Coumadin. His medical history included several episodes of stress-related angina pectoris (five events in five years).

As noted above, there are no details concerning usage, so the subject's consumption of ephedrine cannot be estimated. Tacharrhythmias, including atrial fibrillation, can be induced by high doses of ephedrine due to its cardiac stimulant effects, but such an effect would be short-lived and would abate as tissue levels subsided. In fact, the attending physician notes in the medical record four days after the subject was admitted to the hospital, "if condition triggered by the ephedrine it would have worn off by now." That observation, along with the subject's history of occasional untoward cardiac events, suggest that the atrial fibrillation probably represents the emergence of an underlying cardiac abnormality, rather than a direct effect of the ephedrine product.

(d) ARMS No. 10009:

A 35 years-old male took Metabolift, two capsules at noon and three capsules at 4:30 P.M. He worked out from 5:30-6:30 P.M. and developed chest pain around 7:30 P.M. He was admitted to the hospital and treated with TPA. Cardiac catheterization revealed normal coronary vessels. His CPK was elevated and his EKG was diagnostic for myocardial infarction (inferoapical). There is insufficient information to make an evaluation.

Ref. 149a Table indicates that Metabolift (from another case) contains in two capsules: ephedrine 0.9-2.4 mg. Pseudoephedrine 7.0-7.6 mg, norephedrine (PPA) 0-3.0 mg, methylephedrine 1.1-2.3 mg, for total ephedrine alkaloids of 9.0-15.3 mg. These are modest doses of the alkaloids and would not be expected to cause untoward effects in a healthy adult.

(e) ARMS 10275:

> A 63 year-old female reported using Formula One at recommended dose for three weeks, when she developed hives. The next day she had difficulty walking across room, difficulty breathing and swallowing, and she vomited. She suffered ventricular fibrillation, a small nonQ-wave infarction, and was hospitalized for five days. Cardiac evaluation failed to reveal any heart problem to explain her arrest. She has chronic obstructive pulmonary disease secondary to cigarette smoking.
>
> There is not enough information (documentation of use, medical records) available to make an evaluation. Her pulmonary disease and tobacco use may be contributory.

(5) Blood Pressure Elevations Allegedly Caused by Ephedra Herb Products.

The Proposal reports six examples of elevated blood pressure among the 20-32 million Americans who consumed ephedra herb products during the period when these AER's were being collected. Three of these involved individuals who were being treated for high blood pressure, or had had prior episodes of high blood pressure before beginning to take ephedra herb supplements (ARMS 10991, 11050, 11298). These individuals should never have been taking ephedra products.

All six of these individuals were taking very small doses of ephedrine alkaloids, ranging from 2-10 mg per serving. As Dr. Patrick points out, "[I]t is difficult to believe that such modest doses of ephedrine alkaloids could cause the elevation in blood pressure..." The scientific literature reflects the fact that blood pressure is not affected by single doses of ephedrine alkaloids up to 60 milligrams, some 6 to 30 times what these individuals consumed. E.g., Pental, supra; Chua and Benrimoj (1988); see Dulfano (1973) (no effect on blood pressure of 25 mg single doses of ephedrine); Tashkin; (1975) (same).

The agency has previously accepted the fact that small doses of ephedrine alkaloids, at or below 25 mg, do not pose any risk of increasing blood pressure, in the OTC Bronchodilator Monograph. There, it was argued that ephedrine should not be Category I (safe and effective), because of "some elevation of blood pressure." 41 Fed. Reg. at 38370. The Panel responded that clinical studies in the literature

> showed that a single dose of 25 mg had no significant effect on either heart rate of blood pressure...[S]ystolic and diastolic blood pressure showed no significant change.

41 Fed. Reg. at 38370. Pentel likewise notes from his review of the literature that "doses of ephedrine up to 60 mg generally do not increase blood pressure." Pentel (1984), supra.

So it is very difficult to associate the increased blood pressure seen in these six subjects with ephedra herb supplement ingestion. If the three who did not have prior blood pressure problems actually responded to the low doses consumed, it could only be because they are part of a tiny subpopulation that may be exquisitely sensitive to these alkaloids, much as a limited number of people are at risk in consuming certain nuts.

(a) ARMS 10888. Dr. Patrick concludes:

> This 38 year-old female took Nature's Sunshine SN-X 100 for four days and developed syncope and blood pressure of 180/110 mm Hg. She was seen in the ER with severe headache, nausea and diaphoresis. Regular monitoring for five years prior to this event had revealed no high blood pressure. After stopping the product her blood pressure returned to normal.
>
> Ref. 149a Table indicates that this product contains: ephedrine 1.2-1.4 mg, pseudoephedrine 0.4-0.6 mg, and total ephedrine alkaloids 1.6-2.0 mg.
>
> It is difficult to believe that such modest doses of ephedrine alkaloids could cause the elevation in blood pressure described in this case. However, the reported time course of the use of the product relative to the adverse reaction and the positive dechallenge suggest that the product was involved. There is not sufficient information and documentation to make a complete evaluation.

(b) ARMS 10919. Dr. Patrick concludes:

> A 49 year-old woman used Power Trim, three capsules three times daily, for three weeks. She developed weakness, dizziness, nausea, vomiting, and palpitations, and went to the ER. She was found to have vertigo, serious otitis media bilaterally, hypertension (150/102 mm Hg) and elevated liver enzymes. She reports that after stopping the product, her blood pressure returned to normal without medical treatment.
>
> There is insufficient information and documentation to make an evaluation.
>
> The product (Power Prime per Ref. 149a Table) contains in three capsules: ephedrine 9.4-10.2 mg, pseudoephedrine 1.8 mg, norephedrine (PPA) 0-2.4 mg, and total ephedrine alkaloids 11.2-14.4 mg.

The vertigo, dizziness, and perhaps the nausea in this case are most likely related to the serious otitis media. The hypertension and palpitations are effects typical of ephedrine, but they would not be expected at this dosage in a healthy adult.

(c) ARMS 10946. Dr. Patrick concludes:

A 42 year-old woman used ThermoChrome 5000, one capsule twice daily, for three days. She was also taking vitamin B12 and an antioxidant supplement. She developed a rash and stopped all three products for three days. She restarted the ThermoChrome 5000 and three days after that was found to be hypertensive (170/114 mm Hg). She has no history of hypertension, and one week before starting the product her blood pressure was normal (120/78).

There is insufficient information and documentation to make a complete evaluation.

ThermoChrome 5000 contains (per Ref. 149a Table) ephedrine 2.4-2.5 mg, pseudoephedrine 1.7-1.9 mg, methylephedrine 4.2-6.1 mg, and total ephedrine alkaloids 8.3-10.5 mg. These are low dosages of alkaloids that would not be expected to cause a significant elevation of blood pressure in a healthy adult. However, the reported time course of use and the hypertensive episode, plus the apparent positive dechallenge, suggest that the product may have been involved.

(d) ARMS 10991. Dr. Patrick concludes:

A 54 year-old woman used Tri-Chromaleane, at less than the recommended amount, once daily for "a number of weeks." She was under treatment for hypertension. After starting the product her blood pressure increased and her doctor added a second medication and her blood pressure improved. She stopped the Tri-Chromaleane (after failing to pass a physical exam for insurance purposes) and her blood pressure improved.

There is not sufficient data on consumption nor appropriate medical documentation to permit a complete evaluation of this case. Elevated blood pressure is certainly an effect of ephedrine taken in sufficient dosage, and its appearance and dissipation in this case appear to coincide well with the use and discontinuation of the ephedra, respectively. This mild, reversible reaction is likely to be related to the use of Tri-Chromaleane. This subject, due to her hypertensive condition, should not use ephedrine-related products.

(e) ARMS 11050. Dr. Patrick concludes:

This 63 year-old female took ThermoChrome 5000, two or three pills twice daily, for two months. She was also taking Lescol for hypercholesterolemia, Zantac for esophageal reflux, and Vasotec for hypertension. She developed worsening of the hypertension (174/93 mm Hg) and episodes of palpitations. She sought medical assistance after an especially severe episode of palpitations. After stopping the product her blood pressure normalized (to 140/80 mm Hg) and the palpitations resolved.

There is insufficient information and documentation to permit a complete evaluation of this case. The effects of elevated blood pressure and palpitations are associated with ephedrine alkaloids, and the time course of the effects and the dechallenge in this case suggest that the ephedrine product may have been implicated in those adverse effects. However, the quantity of ephedrine alkaloids in ThermoChrome 5000 (approximately 10 mg total ephedrine alkaloids per serving, according to Ref. 149a Table, concerning another case) is only a fraction of the dose generally required to cause a significant elevation of blood pressure (60 mg, from the clinical literature).

In any case, the subject should not have used ephedrine products while undergoing treatment for hypertension.

(f) ARMS 11298. Dr. Patrick concludes:

This 41 year-old male consumed three herbal products, including Fast Start containing ma huang and guarana, following the labeled instructions, according to his report. He felt that the products gave him a "rush" and caused blurred vision, but there was no medical evaluation or documentation of those reported signs. On the fifth day of use of the products, he noted red-stained urine and sought medical attention. Urinalysis did reveal "moderate" hematuria, and physical examination revealed a blood pressure of 136/102 mm Hg. His hematuria cleared approximately one week after discontinuation of the herbal products, and his blood pressure returned to normal approximately one month after discontinuation.

The self-described "rush" could certainly be attributed to the combination of ephedrine, pseudoephedrine, and caffeine contained in the Fast Start preparation. The ephedrine alkaloids, could also cause papillary dilation which could contribute to mild visual changes such as photophobia. However, these compounds do not

affect lens accommodation significantly, and therefore should not cause a true blurring of vision.

The hematuria that prompted the subject's visit to the hospital is unlikely to be directly related to the effects of the ephedrine alkaloids. Such an effect is not characteristic of the class of compounds, as evidenced by the lack of other reports of this type in the ARMS series. Hematuria could conceivably be precipitated by a hypertensive episode, but a higher blood pressure than was observed in this case would be necessary to cause hematuria.

With regard to the elevated blood pressure observed, the ephedrine alkaloids could cause such an effect. However, such an elevation would not be anticipated a the levels of ephedrine alkaloids consumed. In clinical studies summarized by Chua and Benrimoj (*Medical Toxicology* 3, pp. 387-414, 1988), 60 mg of ephedrine and even higher doses of pseudoephedrine were required to produce a significant effect on blood pressure. According to the "specific consumer intake" reported for this case in the FDA Proposed Rule, Ref. 149a Table, the average serving consumed by the subject contained 6.6-9.8 mg ephedrine and 10.0-10.8 mg pseudoephedrine, levels a fraction of those reportedly required to raise blood pressure significantly in healthy adults.

The subject did have a measured blood pressure of 134/92 mm Hg. approximately eight months prior to the reported adverse event, so it may be that his blood pressure was rather labile and therefore more sensitive to the effects of the alkaloids. However, the fact that the hypertension required a month to resolve argues against a direct effect of the ephedrine alkaloids, because the elevation of blood pressure induced by those compounds is an acute effect that should subside with the decline of tissue levels over a period of a few hours.

In summary, the ephedrine alkaloids consumed in this case cannot be completely ruled out as contributing to the subject's acute hypertension, but it is highly unlikely that they contributed to the hematuria or were a significant factor in his more prolonged hypertension.

(6) Seizures Allegedly Caused by Ephedra Herb Products.

Among the 20-32 million people who consumed some 4.4 billion doses of ephedra herb dietary supplements during the period FDA was soliciting adverse effect reports, the agency has identified only ten instances where an individual allegedly had a seizure. Three of these reports

are impossible to evaluate because they lack any medical information, are highly subjective, and contain little reliable dosage or temporal information. But in each of those cases, the amount of ephedrine alkaloids in the product consumed are so small that there is no reason to believe that level of ephedrine could cause any injury, and nothing in the scientific literature supports seizures at those levels (about 60% or less of the authorized OTC single dose of 25 mg). If these low levels of ephedrine are a threat for seizures, then there should be literally thousands of ephedra-induced seizures reported.

Of the remaining seven cases, the treating physician attributed the seizure, not to ephedrine ingestion, but to other lifestyle factors, in two cases (AER 11078: "pseudo-seizure, probably secondary to fatigue and stress;" AER 11249: seizure secondary to heat, low blood sugar, improper diet, and exhaustion).[41] Two other seizures (AER 11181, 11215) occurred long after the individual had ceased taking any ephedra herb product, so there could not have been any ephedrine in their systems to cause the seizure. In the remaining three cases, it seem clear that the amount of ephedrine in the individual's system was too small to precipitate a seizure, either because of the small amount consumed, or the extended delay between consuming the product and the apparent seizure.

(a) ARMS 9747. Dr. Patrick's analysis:

> A 40 year-old female was reported by her physician to suffer a grand mal seizure after using Ripped Fuel, two tablets twice daily as directed, for three days. Her husband stated that she stopped breathing and he had to administer mouth-to-mouth resuscitation. Her medical history was negative. She had no symptoms except dizziness immediately before her seizure. CT of the head was normal.
>
> There is insufficient information to make an evaluation. There is no documentation of usage and no medical records.
>
> Analysis of Ripped Fuel (in FDA Proposed Rule Ref. 149a Table, related to another case) indicates no detectable ephedrine in the product, and 14.8 mg pseudoephedrine per serving. Therefore, it is questionable whether authentic ephedrine is involved in this case at all. It also seems highly unlikely that this low dose of pseudoephedrine would cause a seizure in an otherwise healthy adult.

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[41] Once again, quotations or comments in the record, suggesting a lack of association between ephedra and a particular patient's condition, were omitted from the discussion of that patient's records in the Proposal (See footnotes 39, 40).

(b) ARMS 10437. Dr. Patrick's analysis:

A 55 year-old female reports a grand mal seizure after use of Thermajetics Herbal Tablets for three days according to directions. She had no significant medical history; CT and EEG were normal. She was taking no medications or other dietary supplements.

There is insufficient information and documentation to make an evaluation.

Thermojetics Herbal Tablets-Green contain in each serving ephedrine 1.8 mg (from Ref. 149a Table, concerning another case). It seems unlikely that such a low dose of ephedrine could precipitate a seizure in a healthy adult. However, the reported time course and nature of the event suggest possible involvement.

(c) ARMS 10974. Dr. Patrick's analysis:

A 19 year-old female consumed ShapeFast, one capsule before each meal, three times daily, for one month. Her family witnessed seizure activity and took her to the ER. CT and EEG were normal, and no risk factors for seizure could be identified. She had no significant medical history and took no other drugs or supplements.

There is insufficient information and documentation to permit a complete evaluation. Seizure activity is a potential effect of ephedrine alkaloids, but the dosage encountered in this case would not be expected to cause seizures in a healthy individual. Alkaloid content of the product was (from Ref. 149a Table) ephedrine 6.9-8.9 mg, pseudoephedrine 4.1-4.2 mg, and total ephedrine alkaloids 11.0-13.1 mg. Also, such an effect would not be expected to emerge after one month of use at constant and continuing dosage.

(d) ARMS 11062 Dr. Patrick's analysis:

This 42 year-old woman consumed Power Trim, two or three capsules before meals as directed, for three months. She was taken to the hospital after family members found her seizing. She had another seizure while being examined by the neurologist. She complained of increased headaches and slow thinking in the days preceding her stroke and was taking penicillin for a dental abscess. CT and MRI showed a small, right-sided intracerebral hemorrhage. MRI and angiography revealed no evidence of any vascular abnormality. She was treated with Dilantin.

period FDA was soliciting AER's, we would expect there to be about 8,000 seizures for which there is no identified cause. Only a comparative handful of seizures supposedly associated with ephedra herb products were reported to FDA, and even accepting the agency's unlikely assumption that 90% of seizures go unreported, there still seem to be far fewer strokes associated with ephedra herb consumption, than are seen in the general population which does not consume these products.

Likewise, with strokes: in 1990, there were 392,344 first strokes. American Journal of Epidemiology: 144: 665-673 (1996). This is an incidence in the general population of 1.45% (392,344 divided by 270 million). Among the minimum number of individuals consuming ephedra herb product even in a single year, 5,000,000, we would expect a stroke incidence of orders of magnitude greater than what FDA has reported. So once again, he comparative handful of strokes among those 5,000,000 individuals who consume 1,100,000,000 doses of this herbal product every year, simply cannot support a "cause and effect" between that consumption and a risk of stroke.

This is of particularly concern here, because FDA associates some anecdotal seizures and strokes with ephedra herbs by a process of exclusion: that is, there was no other obvious basis for the adverse effect. That approach overlooks the fact that in the United States every year, hundreds of thousands of seizures and strokes (and deaths, heart attacks and psychotic episodes, to say nothing of elevated blood pressure) occur which have no documented cause whatever. **The absence of another apparent cause is simply not proof that ephedrine consumption must be responsible for a serious adverse event.**

Third, the Proposal is seriously deficient because it uses, almost entirely, percentages of adverse events or other data, rather than the actual numbers. E.g., Figures 2,3, and text of Proposal. Table 3, for example, displays the percentage of individuals consuming ephedra herbs before suffering an alleged adverse event, but never gives the number of individuals involved. Table 2 breaks down age and gender relationships to adverse events on a percentage basis, but never provides the numbers of individuals involved.

This approach serves to hide the extremely low numbers that are involved. There is so little data on actual ephedra consumption, for example, that the power of inferences drawn from the limited data are nowhere near "robust." They have essentially no predictive power for the population as a whole.

Significantly, nowhere in the proposal does the agency provide any information as to the number of individuals for which there is consumption data, either in the total of all AER's, or among the 53 individuals on whose reports the Proposal rests. Presumably that is because, as careful study of the record shows, less than 6% of the total reports include actual consumption data, and only 11 individuals have that data among the 53 Proposal AER's. It is obviously impossible to base action on 11 individual anecdotal reports.

Fourth, the Proposal seriously misuses the scientific literature, in suggesting that it supports the AER's, when there is not a single study reporting serious adverse events at the dosages consumed here, much less the 8 mg proposed hazardous level.

Fifth, FDA almost completely ignores the fact that if these adverse events will in fact occur at 8 mg doses of ephedrine in dietary supplements, they should occur at the 25 mg doses of ephedrine found safe by the agency under the OTC monograph. To argue otherwise is to stand toxicology on its head. FDA speculates that this will not occur because of differences in the products, user populations, and uses, 62 Fed. Reg. at 30704, but it offers only this speculation and no facts.

There is, for example, no reason to believe that the consuming populations are different; in fact, they may very well overlap, for asthmatics may wish to loose weight. The OTC product is directed at a population that suffers from a serious intercurrent disease. Other things being equal, they may well be at greater risks for death, cardiovascular disease, and other serious adverse events. So the Proposal's argument is at best a distinction without a difference.

There is likewise no reason to believe there are any relevant differences in usage. We have to assume that all of these products, OTC drugs and dietary supplements, are consumed according to label directions. If so, an asthmatic could consume up to 150 mg per day, in 25 mg doses. Those using dietary supplements for weight loss could consume the product's recommendations, which in virtually no case reaches 150 mg total daily dosage, and in many cases (see Ref. 149a) be well below single doses of 25 mg.[46]

Likewise, the suggestion that the respective "products" are different, i.e., have different effects, is completely speculative. While the agency correctly notes that other ingredients may be contained in ephedra herb dietary supplements, it makes no effort to show that these ingredients have any effect of increasing the risk of consuming the ephedrine alkaloids in the dietary supplement.

Absent any evidence that these other ingredients increase the risk, the Proposal makes two arguments. First, it contends that the dietary supplements contain ephedrine alkaloids," while the OTC drugs contain "pure ephedrine." That argument is fine as far as it goes, but ultimately it is another distinction without a difference. For the difference between these two ingredients is that while there are other alkaloids in ephedrine alkaloids, those alkaloids are pseudoephedrine and PPA. Both these alkaloids are OTC approved for safe use at levels higher than ephedrine, so they replace the ephedrine itself which has a lower use level under the OTC monographs. This distinction hardly shows that ephedrine alkaloids are potentially more harmful than synthetic ephedrine. The literature suggests the opposite, both in animals (Pedersen, Tab 12), and in humans (Tab 9, p. 8).

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[46] There is no basis for assuming that an asthmatic, suffering from a middle-of-the night attack leaving him unable to breathe, is less likely to exceed recommended doses than an individual using an ephedra herb product for weight loss or body building.

Second, the Proposal elsewhere suggests that the caffeine which is often contained in ephedra herb dietary supplements, may increase any adverse effects of ephedrine. In making that argument, the FDA seriously misstates the well-known Astrup trial comparing ephedra, caffeine, ephedra plus caffeine, and placebo for weight loss (Tab 8; see Tab 9, p. 8; Ref. 105). The ephedra-caffeine combination did not produce statistically significantly more adverse effects than did the other treatment groups, as the Proposal contends (62 Fed. Reg. at 30696). In fact, at four weeks, all the treatment groups had comparable side effects, which were significantly greater than placebo; but at eight weeks, there was no statistically significant difference between any of the four groups (Tab 8, pp. 22-23; Ref. 105).

Far from showing that the addition of caffeine to ephedrine alkaloids increased side effects, the Astrup study shows that caffeine does not increase the risk. Moreover, the most serious (and also most widespread) side effect in this study was insomnia, not any serious clinical effect (Ibid.).

In short, there is absolutely no evidence that the safety of the OTC 25 mg dosage should not be interpolated to dietary supplements. Indeed, that is essentially what FDA has sought to do elsewhere in the proposal: the agency

> considered it appropriate to rely on evidence from pharmaceutical sources of single ephedrine alkaloids in assessing the effects of botanical sources [62 Fed. Reg. at 30682];
>
> Evidence from pharmaceutical sources [was relied on to assess safety because] once absorbed, the botanical and synthetic sources of ephedrine alkaloids undergo similar metabolic process [62 Fed. Reg. at 30685].

In short, when FDA argues that OTC drug use is irrelevant, it runs into a conflict with science and its own expressed approach in the Proposal.

Finally, these problems developed because of the fundamentally unfair nature of the Food Advisory Committee proceedings, to which the Proposal looks for justification. First, the extensive agency materials were not made available to the Ad Hoc Committee, or others, in advance of the meeting. Second, the vast bulk of the scientific material was presented orally by agency representatives. Third, while FDA was given virtually unlimited time to influence the Committee (Dr. Love, for example, used almost an entire session), others were given only seven and a half-minutes to make their presentations. More importantly, they were not allowed to question the FDA's presentation.

This format was hardly designed for, nor capable of, bringing out the scientific facts behind the safety of ephedra. In particular, the FDA's data and conclusions were never subjected to any peer review (allegedly because of time considerations, but such review still has not taken place more than 15 months later), a process which we believe it could not survive.

We now review in more detail the FAC meeting, before showing that the substantive provisions of the Proposal (7-day use limit, 8 mg dose limit, preclusion of caffeine, and limits on label claims) are unsupported. We close by discussing a number of serious shortcomings of the Proposal.

a. FDA's Data Presented to the Food Advisory Committee.

The best summary of the FDA's presentation to its Food Advisory committee was made by a statistical expert on the Committee, who described himself as "disturbed" by the "lack of either science or scientific quality" in the FDA's presentation. (The Tan Sheet, September 2, 1996, p. 6). He was referring in part to the fact that FDA never made any effort to show that those who consume ephedra herb products suffer any more injuries than those who do not, a basic showing if a product or ingredient is going to be regulated as hazardous. But he was also talking about the general lack of scientific methodology in the FDA's positions.

The obvious deficiencies of the FDA's presentation fall into three categories. First, some committee members "questioned FDA's methodology in collecting and presenting the adverse events data" (Ibid., p. 6). For example, the agency accepted the injury reports, even when they were ridiculous on their face, and even where FDA knew they were invalid.[47] Indeed, while admitting "[m]ost cases [involve] patient factors that make interpretation and attribution of the individual adverse events problematic" (FDA Presentation, Summary Slide), FDA nevertheless "attributed" all the reports to ephedra, and treated them as if they were completely valid to establish that ephedra or ephredine caused a women to develop Lou Gehrig's disease, or another woman to start menstruating at age 76.

FDA sought to justify this approach, in part, by saying that passive reporting systems undercount adverse events. That may be true in some cases, but not here. Beginning with an article in the FDA Medical Bulletin on September 1, 1994, FDA urged health care providers to report all "adverse events with ephedra"; FDA's MedWatch later repeated this call for injury reports on at least two occasions. These were followed by massive FDA-generated national publicity, including several press releases, where the agency warned of ephedrine product hazards. The Texas Department of Health did the same thing, so successfully that over one-quarter of the AER's came from that one state. No wonder the injury reports increased; as the Texas AER's show, many consumers reported adverse events because "there was a news bulletin on Channel 4 that told of serious effects" (AR 005735). One of FDA's 53 AER's cited in the Proposal was reported more than 6 months after it occurred because the individual saw an FDA report on Ephedra.

Moreover, while there may be some possible underreporting of minor symptoms and effects, any serious adverse event – heart attack, stroke, seizure, psychotic event, or death – will involve a health care provider who receives the FDA Medical Bulletin. Serious events are thus

[47] For example, FDA was told in at least seven cases that the product ingested contained no ephedra, but still counted them as ephedra-related injuries (Testimony of Michael Betz).

likely to be over-reported, because (as Dr. Borzelleca cautioned, Tab 3) of the assumption that any temporal connection between consumption and injury is equivalent to a causal connection. At the least, all such serious injuries surely will be routed to state and federal public health officials.

The real flaw in the FDA's methodology was its failure to deal with the issue of cause and effect. "Committee member Bruce Chassey, Ph.D.....emphasized that FDA 'needs to build a cause-and-effect relationship between supplement intake and adverse events. . ." (The Tan Sheet, September 2, 1996, p. 5) FDA had collected some 608 adverse reports, but had no consumption data on 572 of these reports, making it impossible to attribute any injuries to consumption of ephedra herb products at "conditions of use recommended or suggested in labeling" (DSHEA, § 4). In most of the cases, there were so many other likely causes that FDA conceded:

> most cases are complex, with patient factors that make interpretation and attribution of the individuals adverse events problematic. [FDA data summary, p. 14]

Essentially, what he FDA produced was several hundred separate, anecdotal examples of asserted injury allegedly caused by ephedrine containing products, a trivial number among the 5-8 million annual consumers of these products. Such anecdotal reports, especially where they are not carefully investigated, are considered useless to establish a fact in science, whether that fact is a product's safety or lack thereof. That is because each consists of a single-person clinical trial, which lacks the robustness to be predictive of other outcomes, and which cannot be aggregated because the conditions – including past episodes, concurrent diseases, and other medications – of each are so different.

Second, FDA's entire presentation consisted sole of "numerator data" – injury reports devoid of any context provided by evaluating the total population at risk. With only about 600 total reports, fewer than 100 of which involved anything other than expected, minor, transitory effects, the agency presented no "denominator" information. But estimates of the number of Americans consuming ephedra herb products each year ranged from a low of 5-8 million (Testimony of Dr. Jones) to as much as 24 million; in either case, even if the reports were all valid (and most are not), they would represent an almost unmeasureably tiny incident rate, well below that for spontaneous adverse incidents at the same injuries in the U.S. population. Certainly, if the focus is to be (as FDA puts it) on raw numbers of reports, then many familiar consumer and OTC products produce more emergency room admissions, are more often mentioned in autopsy reports, and have a higher instance of young person abuse, than ephedrine.

Third, because the failure to realistically assess cause and effect was so obvious in the FDA presentation, and because the agency assumed such a relationship in all cases, it was particularly important that the data be subject to peer review. But when a member of the FDA committee asked the agency if its conclusions were in a form to be reviewed by independent experts, FDA admitted that they were not. They still are not.

Fourth, while FDA tried to brush aside the clinical data showing that in weight loss studies, very few, only minor, side effects were seen, by arguing that these were not safety

studies, the fact is that no serious adverse events were reported in more than twenty clinical studies where the patients were constantly being monitored for any adverse events by medical professionals. It simply is not credible that the public is at risk from products allegedly reported to cause serious adverse events, when none of the individuals undergoing careful medical monitoring during a clinical trial showed such effects. Recent clinical studies, including the monitoring of more than 800 individuals so fare entered into the St. Luke's open label study, and the initial results at Vanderbilt, likewise show no examples of serious injuries.

FDA also sought to use the clinical studies to its advantage, arguing that the "side effects" had been seen in these trials. That was disingenuous, because no such effects were shown except in high dose, abusive, case reports. As Dr. Denis Jones explained in his literature review, "ephedrine...did not cause increases in blood pressure or heart rate...There were no clinically important side effects in the reviewed studies...Such [minor] effects as were seen...were transient and ceased rapidly...as subjects continued to use the "treatments" (Tab 8, p. 79). There are none of the serious adverse events which FDA believes are caused by ephedrine – such as "healthy people" suffering serious injuries or death after 1 to 5 mg doses – in any of the two dozen clinical studies. These clinical studies undermine the FDA's arguments, rather than support them. Nor are there any such reports of low dose, clinically serious events in the scientific literature.

Finally, the FDA's primary assertion – that very small doses (below 15 mg, and down to 1-5 mg) of ephedrine-containing products pose serious health risks – flounders on the fact that since the early 1980's, FDA's OTC regulations have permitted asthma-compromised individuals to ingest 25 mg ephedrine tablets for up to six time per day. 21 C.F.R. Part 341.76. FDA concedes there are virtually no known adverse events or injuries resulting from this ingestion.

These OTC bronchodilator products are pure ephedrine. They are thus far more potent on an ounce for ounce basis than herbal dietary supplements, which contain no more than eight percent ephedrine alkaloids. If consuming an eight-percent ephedrine dietary supplement at 15-20 mg doses two or three times a day in fact posed a hazard, then surely consuming a 25 mg pure ephedrine drug product for up to six times a day would have produced adverse indigent reports among the tens of millions of Americans who use such products.

This question was put to FDA by a Panel member: "How do you account for the discontinuity between the lack of reports of adverse events from OTC ephedrine products, and your feeling that these dietary supplements are causing all these injuries?" The FDA had no medical explanation for that inconsistency.

In fact, the scientific literature, clinical studies, animal studies, Goodman & Gilman, and the known toxicology of ephedrine alkaloids, show that ephedrine alkaloids have no toxicological effects below a single dose of about 50-60 mg orally. Likewise, OTC drugs containing pure ephedrine at single doses of 25 mg have not produced injury reports, as they would not be expected to, if ephedrine were hazardous at the 8 mg single dose in the FDA proposal.

In the face of this medical science, FDA could only point to the tiny collection of unevaluated injury reports, to support its argument that ephedra herb products are somehow a

risk. These are some of the cases on which – without data as to the amount consumed, and in some cases without knowing whether the individual consumed any ephedra – FDA accepted as showing that ephedra herb products are hazardous:

- Seven cases where the adverse events occurred when the individual was not using an ephedra product (8904, 9144, 9483, 10248-50, 9864);

- Numerous cases where the adverse event occurred previously, when the individual was not taking an ephedra herb product (8889, 9060);

- Numerous cases where the adverse event continued after discontinuation of the ephedra herb product (9606, 9809, 9815, 9060);

- Several cases where no adverse effect was listed (10067, 10075);

- Numerous reports filed by "friends" of the person allegedly injured, with no details, and in some cases, no specific injury (8842, 8893, 10244,10802);

- Many events medically unrelated to ephedrine ingestion (8331, 9505, 9726, 9925, 10258, 10313, 1033, 10505);

- Numerous cases where concurrent medications or an underlying condition is a more likely cause of the injury (8889, 8896, 9253, 10042); in a number of cases, the party was found to have amphetamines in his blood (9322, 9324, 9507);

- Some bizarre causation claims accepted by FDA:

  + "Shot and killed a store clerk" (11096);

  + Pharmacist letter "not linked to particular customers" (8893);

  + Unknown: "dose/duration, and if [taking product] at time of Adverse Event" (9188);

  + Pharmacist complained about "14 year old taking for obesity" (9874)

  + Got "pregnant through using Norplant" (10258);

  + 76-year old "started menstruating" (10338);

  + Attempted suicide by taking 19 pills (10378);

  + Case of impotence "reported by attorney, without any details;" and

+ "Erection of penis, sustained" (11153).

b. FDA's Proposed Limitations On Ephedra Dietary Supplements.

The Proposal would place substantial limitations upon products containing ephedrine alkaloids, including ephedra herb dietary supplements, while leaving OTC drug products with higher levels of these alkaloids on the market. While not imposing prescription drug status upon these products, FDA's regulation would (1) limit use to no more than seven days, thereby eliminating all weight loss claims; (2) limit the ephedrine alkaloid content to less than 8 mg; and (3) forbid the addition of caffeine to ephedrine. These limitations are based upon a fourth point: (4) the products are hazardous unless these limitations are complied with.

These is not a shred of medical or scientific evidence supporting these limitations, and a substantial amount that is contrary to them. Indeed, FDA all but concedes that its conclusions are not supported by the scientific literature, animal studies, any reports of adverse events from ephedrine drugs, or clinical studies. Instead, its proposal rests entirely upon its analysis of the defective injury reports its received, few of which had any information as to how much the individuals consumed (36/602 (6%) at the F.A.C. meeting), (11/53 (20.8%) of the ARMS in the Proposal).

Dr. Graham Patrick of the Medical College of Virginia reviewed the FDA proposal, studied a number of the articles cited by FDA, and has looked at a substantial amount of the injury report material. He concluded that the FDA's conclusions "lack rigorous medical documentation or sound scientific rationale for their bases." (Tab 1).

1) FDA's Limitation to Seven Days' Use.

Ephedrine has a half-life in the body of about four hours, i.e., half of it is excreted in four hours, another half in the next four hours, etc. Thus, it does not build up in the system, so it poses no risk for long-term toxicity. After about four days of use, its level remains constant in the body, not increasing with further dosage. Limiting its use to seven days would not reduce any risk of injury, nor is it consistent with ephedrine's known pharmacokinetics.

FDA claims to have seen "patchy necrosis" (partial death of the heart muscle) in one individual who took ephedra herb products at recommended doses for one year (ARMS 11134), as the sole scientific basis for this limit. However, that is the only such incident ever recorded, and it cannot be related to ephedrine. To support its conclusion, FDA states that such cases are reported in the scientific literature, citing three articles

However, as noted above in the Table (p. 58), the first report cited was of a woman taking about 500 mg ephedrine for ten years; her cardiac condition was reversed. The second report was of a woman who took 2000 mg daily for eight years; she also survived. The third report involved a man who had taken 400 mg daily for sixteen years; he likewise survived. All the articles describe use at these levels as "abuse," chronic," "excessive," "heavy," and "much greater than

the maximum recommended dose." Thus, even these long-term ephedrine abusers did not die, and there is no indication that, since they survived, they suffered from "patchy" heart muscle necrosis.

In addition, as Dr. Patrick points out:

- The limitation is illogical in terms of the known pharmacokinetics of ephedrine, and is not documented in the scientific or medical literature.

- Peak ephedrine levels are reached within 1 to 4 days, and after 7 days at the recommended dosage; thereafter no further accumulation occurs, and no long-term toxic effects have been determined.

- Any subsequent adverse event would not be "temporally related" to ingestion of ephedra herb dietary supplements, thereby suggesting another cause for the injury.

- Ephedrine containing drug products are not labeled for limited duration because continued consumption does not create the risk of an adverse event. [Tab 1]

The limitation on usage to 7 days is illogical in terms of the known pharmaceokinetics of ephedrine. No such limitation is documented in the scientific or medical literature. With regard to the pharmacokinetics of ephedrine, absorption of ephedrine begins within minutes after oral ingestion, and peak concentration in the plasma is obtained within 1 to 2 hours. Thus, any acute effect is of a single serving of ephedrine would be expected to be evident between 15 minutes and 3 hours after ingestion (and more likely, within 30 minutes to 2 hours). The plasma half-life of ephedrine is variously reported to be an average of 4 to 6 hours, with ranges of 2 to 12 hours reported in some "normal" individuals.

Pharmacokinetic theory (the "plateau principle) states that, with repeated administration of a compound on a regular dosing schedule, the maximal accumulation of the compound, or the "plateau" level, is achieved within 5 to 7 half-lives; that is, no further accumulation above that plateau takes place even though dosing is continued at the steady rate. Therefore, in the case of ephedrine, the maximum concentration of active compound will be attained within between 1 and 4 days of ingestion on a regular schedule, and there is no increased accumulation of ephedrine beyond that time. Thus, any acute or subacute effects of repeated servings of ephedrine would be expected to be observable between the second ingestion and four days of ingestion, during which time accumulation would be occurring.

There is no persuasive evidence for any cumulative effects of ephedrine on the cardiovascular or central nervous systems with chronic ingestion of the recommended dosage of ephedrine for weeks, months, or even years. The FDA proposal justifies the 7 day limitation by citing data which indicate that 60% of the reported adverse reactions to ephedrine-containing products occurred after more than 7 days of exposure, i.e. at a time when ephedrine concentration in the plasma has been stable for at least several days, or, in many cases, several weeks or months. It would not appear that there cases meet the FDA's criterion of a temporal relationship to

ingestion of ephedrine, since the injuries supposedly occurred nowhere hear the time of peak exposure. In fact, the appearance of effects long after a steady-state concentration of ephedrine has been established suggests that those effects have some other cause rather than ephedrine, since the injuries supposedly occurred nowhere near the time of peak exposure.

The few serious events sometimes associated with longer term exposure to ephedrine alkaloids, i.e. a small number of psychoses and an exceedingly small number of cases of cardiomyopathy, have occurred with months or years of use, and in virtually all cases of psychoses and in all 3 cases of cardiomyopathy, at dosage far in exceed of that recommended in either dietary supplements or pharmaceutical preparations (i.e., 450-2000 mg day).

In summary, there is no documented evidence to support, nor even a theoretical reason to believe, that prolonged or chronic ingestion of modest doses of ephedrine (below the FDA over the-counter maximum of 150 mg/day) promotes any greater incidence of serious adverse events than does 7 days of ingestion. Put another way, there is no scientific basis for believing that limiting consumption of ephedra herb products to seven days would prevent or reduce adverse events.

Finally, given the fact that there is no pharmacological or toxicological basis for this limitation, we believe the FDA's only point is to prohibit "weight loss" claims for ephedra herb products. The agency cannot otherwise limit those claims under DSHEA, because they are clearly structure and function claims under Section 6, and because they are well substantiated. But because the seven-day limitation is insupportable, the Proposal to limit claims for uses requiring more than seven days' duration, must also fall.

2) FDA's Limitation to Less Than 8 mg.

FDA has no basis, even in its own data, to conclude that ephedra herb products containing 8 mg or more ephedrine alkaloids present a "substantial or unreasonable risk' to health. Starkly put, FDA has only a handful of reports where there is any information about the amount of product the consumer ingested; such data is available only in 11 of the 53 AER's relied on in the Proposal, which in turn reports only 13 cases where the amount consumed was less than 15 mg. It is impossible to draw any conclusions from such limited data, particularly where the literature repeatedly demonstrates that single doses as high as 50-60 mg are safe. In addition several dozen weight loss studies show no serious adverse effects at single doses of 25-50 mg.

The Proposal assumes (62 Fed. Reg. at 30682, and elsewhere) that synthetic ephedrine and the ephedrine contained in an ephedra dietary supplement have the same toxic properties (and a small amount of literature suggests that the natural ephedra product produces lower but more continuous blood levels) Therefore, it is impossible that the FDA-approved, OTC drug product is safe at 25 mg up to six times per day, while the dietary supplement product is hazardous at only 8 mg three times a day. FDA is proposing to permit fewer ephedrine alkaloids in dietary supplements on a daily basis, than it has allowed in a single dose of the pure drug for unlimited periods of use. This makes no sense, except as "political" science, not medical science.

In short, there is absolutely no evidence that a 25 mg single dose causes more injury that FDA's proposed dosage of less than 8 mg. Likewise, there is also no evidence that anyone who consumed an 8 mg dose of ephedrine alkaloids suffered injuries, or that this dose produces injuries at a rate or to a degree greater than that seen in someone who does not consume these supplements.

Finally, the OTC approval indicates that FDA considers those limits to be safe for self-medication. In fact, there have been few if any reports of serious adverse effects with pharmaceutical preparations containing ephedrine during decades of use, and then only at highly exaggerated, abusive levels (e.g., Tab 66-68). One author reports that through 1985, there was not a single death resulting from the labeled use of ephedrine. (See also Tab 16: There is "not even one article [the literature] documenting [a] human death caused by Ephedra (or linking a death to its use."))

Similarly, there are FDA-approved single doses of 60 mg for pseudoephedrine and 75 mg for phenylpropanolamine (norephedrine), the other "ephedrine alkaloids," for OTC use. It is nonsensical to limit the total of these compounds in an herbal preparation to far less than the limits of each, individually, available in the open market as pharmaceuticals. Many of the articles FDA refers to as showing injuries from "ephedrine alkaloids" involved pseudoephedrine or PPA, neither of which FDA is proposing to take off the market. (E.g., Refs. 60, 62-63, 65, passion); there are more references to PPA injuries than ephedrine.

The principal justification for the 8 mg limit in the FDA proposal are (1) "seven reports of clinically serious adverse events were associated with products that contained 10 to 15 mg per serving," and (2) several supporting articles from the scientific literature. However, as discussed infra, then cases cannot be linked causally to ephedra, and seven cases from a minimum of 20 million individuals consuming doses in this range and higher, is a very low incidence of serious effects. One would expect spontaneous effects (those with no apparent cause) to be much higher.

Finally, data from clinical studies concerning the effects of ephedrine on body weight and blood pressure, and data from poison control centers concerning excessive ingestions of ephedrine products, indicate that far greater doses of ephedrine – from as little as 3-fold to more than 100-fold greater than the FDA proposal – have been consumed by large numbers of people without precipitating any serious adverse reactions.

The FDA proposal itself makes no distinction between incidence of adverse effects at 10 mg per serving and the OTC-approved dosage of 25 mg. The only apparent basis for the selection of 10 (-2) mg was that no "serious adverse effects" were reported at lower doses, although 'clinically significant effects" were attributed by FDA to doses as low as 1 mg. The "scientific" information provided in the Proposal is insufficient to establish that a 25 mg dosage per serving is any more dangerous than the 8 mg limit recommended in the proposal.

3) FDA's Limitation on Combining Ephedra with Caffeine.

There is no indication that the addition of caffeine to an ephedrine product increases the risk of injury. Indeed, in a study to which FDA refers, Astrup (Ref. 105) there was no significant difference in mild side effects between products containing caffeine, ephedrine, or a combination of the two. Eight weeks into this study, side effects were identical in the placebo and ephedrine and caffeine groups. And the author of the study, Dr. Astrup, confirmed that the addition of caffeine to ephedrine did not increase the risk.

Finally, if caffeine rendered otherwise safe ephedrine alkaloids hazardous, then FDA would long since have included warnings or cautions not to consume caffeine, on all OTC products containing ephedrine, pseudoephedrine, PPA, etc. The agency has not done so, because the amount of caffeine in ephedra herb dietary supplements ranges between ½ to one cup of coffee. This trivial amount of caffeine is completely unlikely to turn safe ephedra herb products into "killers," and its prohibition in dietary supplements pointless, because of the high intake of caffeine from other sources.

c. FDA's Scientific and Other Errors Contained in the Proposal's Preamble.

We have previously discussed a number of serious scientific and other shortcomings in the Proposal and its Preamble, in the context of explaining why there is no scientific basis for the limitations FDA proposes on ephedra herb dietary supplements. We now turn to other errors and misstatements which characterize the Preamble.

First, the proposal is not limited to products which contain ephedra herbs. Rather, any injury associated with a product "suspected of containing" ephedrine alkaloids (62 Fed. Reg. at 30680), has been used by FDA to support its position. Even when that suspicion is unreasonable, indeed, even when it has been contradicted (Testimony of Michael Betz), FDA still relies on it. This substantially skewers the AER's, making them difficult to respond to, particularly since FDA does not identify which reports related to products only "suspected" of containing ephedra herbs.

Second, FDA's tabular materials, especially Ref. 149a, only attempt to reconstruct the amount of ephedrine alkaloids in a given product. He agency has almost no data on how much of the product was actually consumed by a given individual. This makes in impossible to satisfy the standard imposed on FDA by Congress, for finding a product a hazard: when it poses a substantial or unreasonable risk "under conditions of use recommended . . . in labeling." DSHEA, § 4. The fact of the matter is that FDA has no idea whether its AER's follow from an underdose, an overdose, or consumption at a labeled dose. Failing that, there is no basis for the agency's Proposal to, effectively, ban the sale of ephedra herb products.

Third, the agency is simply wrong when it states that ephedrine alkaloids "have a history (in the amounts likely to be found in dietary supplements) of being able to product the types of serious of adverse events being observed" (62 Fed. Reg. at 30682). **Nothing in the scientific literature supports that statement.** Indeed, the thrust of that literature is that ephedrine

alkaloids are safe at single doses of 50-60 mg., more than twice "the amounts likely to be found in dietary supplements."

Fourth, the agency included AER's from individuals who had intercurrent diseases, or who where simultaneously taking prescription drugs, that would be far more likely sources of an adverse event than ephedra. FDA likewise listed AER's where the individual who took the product either ignored a warning, or consumed a product he never should take given his physical condition. E.g., three of the six individuals who suffered heart adverse effects, were already being treated for serious heart conditions.

Fifth, the FDA Preamble refers to the "chronic effects of ephedrine alkaloids . . ." (62 Fed. Reg. at 30684). There are no such things; ephedrine's effects are acute, not chronic, and the alkaloids do not build up in the body, even with regular dosage.

Sixth, the Preamble states that the ephedrine clinical trials document "that clinically significant adverse effects can occur" (62 Fed. Reg. at 30688). That statement, also, is false: there is not a single significant adverse effect (stroke, heart attack, seizure, psychosis, death) reported in any of the weight loss trials (See extended discussion in Tab 8).

Seventh, while FDA claims the AER's provide "evidence of the correct [temporal] relationship" (62 Fed. Reg. at 30690), in well over half of its 53 cases, such a temporal relationship does not exist. That is because the person either was not taking ephedra when the effect occurred, or had been taking the product at the same dose level for an extended period of time.

Eighth, FDA claims that there were 'life-threatening" adverse events at 8-9 mg consumption levels, and serious adverse events at less than 5 mg. But it never provides any information to support these bald statements, which are completely at odds with the scientific literature. How many such events took place?; what were the injuries?; which individuals were harmed?; how much was consumed? These basic facts, necessary for the industry to reply to these contentions, is unfortunately lacking in the Proposal, probably because they do not exist. (Since, elsewhere in the Proposal, FDA acknowledges having only four reports at 8 mg. and lesser consumption, 62 Fed. Reg. at 30706, these "life threatening" and "serious" events cannot constitute even a handful, assuming they exist at all.)

Finally, the Proposal involves a great deal of assumptions, as well as some serious number twisting. FDA concedes that

> the nature of the available evidence did not allow specific cause and effect determinations for the majority of individual reports.

(62 Fed. Reg. at 30707). In other words, in most cases FDA cannot assert that ephedra was involved in whatever the AER was. That assumes, of course, the AER was truthful, but even FDA acknowledges that a "certain number of false reports might be expected" (presumably,

including the AER that a women developed Lou Gehrig's disease from consuming ephedra). 62 Fed. Reg. at 30707.

To bridge this factual gap, FDA assumes the presence of ephedra in a product or person because the AER reflects a "similarity" to symptoms FDA associates with ephedrine ingestion (62 Fed. Reg. at 30707).

These comments show the FDA Proposal for what it is: full of sound and fury, but actually signifying nothing. It

- Assumes products "suspected of containing" ephedrine actually contain ephedrine alkaloids;
- Assumes consumption was within labeled doses, when only 11 of its cases had dosage information, and at least two of those exceeded consumption;
- Assumes a causal connection between ephedrine and any and all AER's, even though that is an impossible in over half the AER's;
- Assumes are cases are truthfully reported, while acknowledging that "false" claims will be submitted;
- Assumes that an individual was injured by ephedra simply because he has symptoms similar to those seen after using extremely high doses of ephedra.

There is no science to support this Proposal, so the agency, perhaps understandably, must substitute this web of assumptions and suppositions.

* * * *

There is abundant evidence of the safety of ephedrine alkaloids at the 25 mg doses customarily used, in the scientific and clinical literature, the animal studies, and the OTC approval at that dosage. The Proposal ignores that evidence, focusing instead solely on a relatively small number (53) of AER's, most of which are not causally connected to ephedra herb ingestion, and only 11 of which have any actual consumption data. It misuses the scientific literature by suggesting it supports serious adverse events, when there are none reported at the low doses at issue in this proceeding. And it has absolutely no scientific basis for its 8 mg dose level and 7-day dosing limitation, while its position on the assumed additive limits of caffeine is belied by the study it cites and by the study's author.

The Proposal should be withdrawn.

Sincerely,

THE AD HOC COMMITTEE ON THE
SAFETY OF DIETARY SUPPLEMENTS

By: William D. Appler, M.A.
Executive Director

SEPARATOR PAGE

Misc

ARMS No. 9101

This 33 year-old female used Thermogetics Herbal Tabs-Green twice daily from 11/93 to the first week of 1/94, when she began experiencing dizziness, numbness of left arm and forehead, weakness of legs, shortness of breath, and shakiness. On 1/12/94 she had a bad spell with loss of motor control of right arm, weakness, dizziness, and facial numbness, and stopped taking product at this time. However, spells continued with increased frequency and duration. On 1/30/94, she was seen in the ER for dizziness and tachycardia. She was diagnosed with labyrinthitis and was discharged on Antivert. On 2/2/94 the episodes worsened, she complained that "episodes seemed to occur at the time she was scheduled to take pills." She entered the hospital and had an extensive workup. The diagnosis was SVT (supraventricular tachycardia), and she was discharged on Tenormin and Ativan. She smokes one pack of cigarettes a day.

Although ephedrine could cause the symptoms of dizziness and tachycardia, it would be very unlikely to do so at the doses consumed (estimated to be 1.8 mg ephedrine per ingestion, based on analysis of the same commercial product associated with another case.) Further, the tachycardia was not described until more than two weeks after the last use of the product. The fact that the symptoms not only persisted, but worsened, for several weeks after discontinuation of the product effectively negates consideration of the product as a causative factor.

ARMS No. 9754

A 44 year-old female, reported by physician's assistant to be taking Shape-Fast (400 mg) twice daily, when she developed heat stroke, chest and back pain, hyperthermia and tachycardia while exercising.

There is insufficient information to make an evaluation. There is no documentation of use and no medical records.

According to Ref. 149a Table, each 400 mg capsule contains ephedrine 4.0-4.3 mg and pseudoephedrine 4.5-4.8 mg. These are low doses that would not be expected to cause untoward effects in a healthy adult.

ARMS No. 10063

A 22 year-old woman used Super Diet Max, one tablet twice daily, for several months. On the day of the adverse reaction she took two capsules (?), one A.M. and one P.M., and experienced "increased blood pressure, pounding heart, nausea and vomiting" lasting 1.5-2 hours. The symptoms abated after she discontinued the product (presumably at the time of the adverse event.) She had begun therapy with Prozac two weeks prior to the adverse reaction, and she also reported "drinking lots of caffeine."

Both the data concerning use and the medical documentation are insufficient to evaluate this case fully. For example, the elevation of blood pressure, the only objective sign reported in the complaint, is only self-reported and is not documented by clinical observation. However, the described signs are consistent with the pharmacological effects of ephedrine. The probability of those signs occurring at the dosage of ephedrine apparently consumed is low (approximately 13.5 mg per ingestion, based on the product label and usual strength of standardized extract), but the possibility of an additive drug interaction certainly exists. There is potential for interaction with caffeine, or for caffeine to be the immediate cause of the effects, since the subject was consuming kola nut extract (205 mg per dosage unit, caffeine content unknown) and much beverage caffeine. Also, the recent initiation of Prozac therapy could contribute to an interaction. The possibility of an interaction with Prozac seems particularly plausible for two reasons. First, Prozac is a long-acting antidepressant which requires one to two weeks of administration to reach its plateau in the plasma (corresponding to the two weeks of Prozac treatment prior to the reaction.) Secondly, other adverse reactions have been reported in individuals taking serotonin reuptake inhibitors (such as Prozac) with ephedrine, although most of those reactions have involved a worsening of psychiatric condition.

This relatively mild and reversible reaction may have been due to an interaction between ephedrine, caffeine, and Prozac, with the precise role of any single component being difficult to discern.

An additional note: The medical records indicate that the subject's physician prescribed Fastin (phentermine 30 mg) as an appetite suppressant for her on 5/1/97. If she indeed took that product in combination with Prozac without adverse effects, that would argue strongly against ephedrine contributing to the adverse event described in the complaint. Phentermine is a controlled substance (Schedule IV) with considerably greater sympathomimetic potency than ephedrine.

ARMS No. 10943

A 37 year-old female consumed Omnitrim Tea, two teaspoonsful three times daily, and Omni-4 (a vitamin), once daily, both as directed, for one week. She stopped use of the products due to development of shakes, sweats, racing heart, and loss of hearing in her right ear. Her symptoms resolved after stopping the products, and no significant medical history is reported.

Unfortunately, the only information available in the record was the subject's report. There was no documentation of any medical records, no data concerning use or contents of the products, nor information concerning the time of appearance of symptoms relative to the dosing schedule.

Except for the loss of hearing, the symptoms described could be attributable to acute effects of ephedrine alkaloids in sufficient dosage. Those effects are sufficient cause to discontinue use of the products, but they are not serious and are reversible after termination of use.

ARMS No. 10957

A 34 year-old female used E'OLA AMP II Pro Drops, according to label directions, off and on over a two-year period. She developed "triple vision", lasting a few minutes, and returning three days later, accompanied by vertigo. She was seen in the ER, where examination and CT scan were normal, and she was diagnosed with dehydration. She spent three days in bed with severe vertigo, nausea and vomiting. Subsequent MRI showed multiple bilateral cerebellar infarcts, but no source of embolization was identified. Other workups were unremarkable.

There is insufficient information and documentation to make a complete evaluation. However, severe vertigo and visual disturbances are not typical effects of ephedrine alkaloids. Also, the sudden appearance of the symptoms in the absence of radical changes in use of the product suggest a cause other than the product.

ARMS No. 10960

A 16 year-old female used Blast and Burn as directed on the package for several weeks. Within the first week of use she was taken to the ER with a racing heart. She had several similar episodes. Symptoms resolved when she stopped taking the product.

There is insufficient information and documentation to make a complete evaluation. The nature of the event (racing heart) is characteristic of ephedrine alkaloids, and the temporal relationship of the adverse effect to use of the product as well as the apparent positive dechallenge suggest that the product had a role in this rather mild and reversible effect.

ARMS No. 10977

An 18 year-old female took four pills of an ephedrine-related product (variously described as Emphora Ecstacy, Euphora Ecstacy, and Ultimate Xphoria in the report) on one occasion, to get "high". Two hours later she experienced dizziness and racing heart. She was unable to sleep most of the night. She passed out in the shower the next morning, falling and hurting her neck and back. She went to the ER, where the only abnormality found was a low serum potassium. She described previous episodes of dizziness, always in the morning, but had never before lost consciousness. She reported the adverse event one month after its occurrence, in response to seeing a television report concerning ephedrine.

The dizziness and racing heart two hours after consumption of the ephedrine product, and the insomnia for the next several hours, are almost certainly attributable to the consumption. The time course of effects suggests a causal relationship, and the cardiac and central nervous system stimulant effects are consistent with the pharmacology of ephedrine at rather high doses such as consumed in this case.

The signs exhibited the following morning are not clearly related directly to the consumption of ephedrine. The loss of consciousness is too far removed from the time of consumption to be a direct effect, but it could be due to her lack of sleep combined with her characteristic morning dizziness. The hypokalemia may have also contributed to the syncopal episode, but that effect is highly unlikely to be due to ephedrine. The examining physician described the fainting as "possibly drug-related, sleep deprivation". An EEG performed approximately six weeks after the reported event was abnormal, with "focal mild intermittent temporal erratic slowing". This prompted the physician to conclude that the subject may have an underlying seizure disorder.

ARMS No. 10990

A 58 year-old man consumed Tri-Chromaleane, three pills once daily, for six weeks. He developed memory problems, having difficulty remembering names, familiar phone numbers, and how to perform tasks at work. He stopped the product and his symptoms resolved over the next two weeks. At the same time he had been participating in a clinical trial of Proscar for prevention of prostate cancer, and he does not know if he received Proscar or placebo. The study director reported that it was unlikely that the subject's complaints were related to Proscar.

There is insufficient information and documentation to make a complete evaluation in this case. Considering the pharmacologic effects of ephedrine, it is unlikely that the memory loss is related to it, either. Memory deficits are characteristic of depressant drugs (e.g. benzodiazepines) rather than stimulant drugs. Indeed, there is some suggestion in the literature that some adrenergic stimulants (primarily alpha stimulants) may actually enhance memory. Further, there are no other complaints of similar effects on memory in the present Record. It is conceivable that there may have been some interaction between Proscar and ephedrine that caused this adverse effect, although the nature of such an interaction is difficult to imagine. A rechallenge with the product would be the most likely means to determine if it contributed to this effect.

ARMS No. 11065

A 23 year-old female used Thermo Slim, one tablet three times daily before meals (along with The Accelerator Guarana), for eight days. On the ninth day (4/20/96), she forgot her noontime dose. She thought she might be going into withdrawal, took another dose, vomited, and went to the ER with complaints of racing heart, dizziness, lightheadedness, nausea, numbness of the face and arms, and disorientation. She was advised to stop use of the products, and her symptoms resolved over the next week. The complaint was filed on 5/8/96.

This case is difficult to evaluate due to gaps and inconsistencies in the available information, but it fortunately appears to be a trivial case. It is unclear whether the signs that the subject attributed to "withdrawal" are the same or different from the ones that led her to go to the ER. There is no record of the time that the dose was taken to alleviate the withdrawal, nor of the time of the vomiting after that dose (so it is unknown whether any absorption of the contents of that ingestion would have been absorbed.) Similarly, it is not known how long after those events the subject arrived at the ER. With regard to the symptoms, there is also inconsistency. The medical record from the ER describes only lightheadedness and nausea; the other symptoms are listed only in the complaint and are not documented.

Dosage information is also spotty. The labeling of the products seems to indicate that there should be approximately 5 mg ephedrine per tablet, a quantity insufficient to cause any of the reported signs or to cause any degree of dependence. Caffeine dosage from the guarana is similarly uncertain, but caffeine seems a more likely contributor to the effects than ephedrine.

Symptoms are described as resolving over the next week. If symptoms were truly attributable to ephedrine, they should resolve

in less than 24 hours, not seven days. This is a compelling argument against any role of ephedrine in the complaint.

The attending physician stated as his impression: "nonspecific symptoms, without any findings to suggest any acute process." There is no implication of the ephedra product, and that seems a reasonable conclusion.

ARMS No. 11081

A male (presumably young but no age given) consumed Herbal Ecstacy, ten pills on one occasion, to get high. He states that he "became psycho", was very active, developed a "bad mood", and "beat the crap out of a friend." The symptoms resolved, and there has been no further use.

There is no information available concerning this case except for the self-reported complaint. Also, the incident occurred between six and twelve months prior to the filing of the complaint, so the reliability of the account is questionable.

High doses of ephedrine may trigger psychotic episodes. Although the dose and the precise time course of events in this case are uncertain, it is probable that the intentional use of an excessive dose of ephedrine alkaloids was the precipitating event in this adverse reaction.

ARMS No. 11107

A 42 year-old male consumed Diet Fuel, three pills in the morning, for approximately nine months. After taking the product one morning (apparently one to two hours after ingestion) he became dizzy and nauseated with left-sided chest pain, and passed out during a meeting, moments before he was due to give a presentation. His pulse rate was in the thirties. He was hospitalized. His medical history included a similar episode "many years prior", which was diagnosed as epilepsy and treated with Dilantin. His history also included cardiac arrhthmias, prostate enlargement, stress, sleep apnea, and gastoesophageal reflux disease. The diagnosis was "abnormal vasodepressor response to tilt plus catecholamine administration," and the subject was placed on Tenormin.

The labeling for the product has a warning against use by anyone with a history of heart disease or prostate enlargement, so the subject should not have been using this product due to his history of arrhythmia and prostatic hypertrophy.

The signs of dizziness and nausea that he experienced are not uncommon; but chest pain, presumably due to cardiac stimulation, should occur only at much higher doses. The diminished pulse rate is certainly not a typical effect of ephedrine, and is in fact the opposite of the increase in heart rate that would be anticipated. That is why the physician termed the response an "abnormal vasodepressor response". It is also notable that the evaluating physician described the subject as being "under moderate stress at work and extreme stress at home," suggesting that endogenous catecholamines associated with stress may have contributed to the response.

On interview with an investigator, the attending physician stated that he "does not believe the the product caused the illness that _____ experienced, but is not ruling out the possibility." That is a reasonable and cautious conclusion. However, the fact that the subject had used the product without any significant change in

pattern or regimen of use for nine months (and no change on that day) argues against the product being the precipitating cause as opposed to the acute stress that the man was undergoing.

ARMS 11109

This 46 year-old female consumed two E'OLA products twice daily for 1 1/2 weeks. She developed a heart rate of 200 beats per minute (by self-report) and sought medical attention. Medical records describe "evaluation for recurrent paroxysmal palpitations for 20 years." Tests revealed no underlying cardiac disorder.

Lack of documentation is a major problem in attempting to evaluate this case. According to the investigative report, medical records were obtained, but they are not available in the Record. First, there is no medical documentation of the tachycardia (200 beats per minute) that prompted the subject to seek medical attention. That rate was self-reported and was not verified by medical personnel (or verification was not available.) Considering that the subject has a 20-year history of "recurrent paroxysmal palpitations", it is impossible to determine whether or not the reported event is any different from prior episodes. Secondly, the results of tests that were included in the record were too far removed from the reported event to evaluate their relevance to that event. For example, an EKG performed approximately six weeks after the adverse event indicated "sinus bradycardia", an entirely different problem than that described by the subject. Later tests (approximately two months after the event), including EKG, echocardiogram, and exercise stress test, failed to reveal underlying cardiac disorder.

If an adverse effect did indeed occur, it was a transient and reversible effect, and whether ephedrine alkaloids contributed to it or not cannot be determined.

ARMS No. 11112

A 34 year-old female used Thinner Jizer, gradually increasing dosage as directed to two pills in morning and one in P.M. After three days at the highest dosage, she developed jitters and was advised by the distributor to decrease dosage. She took one pill A.M. and P.M. for three days, then developed acute visual changes in her right eye, lasting 25 minutes. Her eye doctor told her the symptoms (difficulty in focusing, a "silvery fish moving in front of eye") were likely due to a vascular spasm, possibly related to her use of ephedrine. She stopped use of Thinner Jizer, took aspirin daily for one week, and has had no further episodes.

Although ephedrine could cause such a vascular spasm in especially sensitive individuals, it would not be expected to cause such an effect in a normal healthy individual at the doses contained in dietary supplements (though the ephedrine content of the preparation in question is unknown.)

According to the clinical summary in the FDA Proposed Rule, this subject had no significant prior medical history. However, review of the pertinent medical records included in the Record revealed that she had suffered trauma to the right eye (a b.b. shot in the eye) as a child and that she had a similar episode of visual disturbance two months prior to the reported event. In fact, the doctor suggested stress, hormonal changes associated with weaning from nursing her child, hypoglycemia, trauma to the eye as a child, or slight trauma (as well as ephedrine use) as potential contributing causes for the visual disturbance.

In summary, it is possible that ephedrine contributed to this event, but it is far from certain that it did. In any case, the event was mild, short-lived, and reversible.

ARMS No. 11114

A 16 year-old male consumed Herbal Ecstacy, two pills on one occasion. Thirty minutes later he was driving the wrong way down a one-way street and feeling "a major rush, tingly, hyper."

There is no information available other than the self-report, so dosage cannot be determined and effects cannot be confirmed by medical records. The subjective feelings of "rush, tingly, hyper" are potential acute effects of ephedrine alkaloids and are probably related to the ingestion. Cognitive impairment, such as would account for errant driving, is not a typical effect of ephedrine and is unlikely to be directly related to the ingestion.

ARMS No. 11131

A 20 year-old male consumed Herbal Ecstacy, five pills, and Nirvana, 6 pills, on one occasion for recreational purposes. He went to a club and felt dizzy, lightheaded, and nauseous, with stomach cramps, thirst, and "a real bad headache." He also felt as if he were going to pass out, started "seeing things", felt his seeing and hearing were distorted, and experienced shortness of breath, sleeplessness and hives. All symptoms resolved by the next day.

There is no documentation of usage, of ingredients in the preparations purportedly consumed, nor medical records of reported effects. Although the subject reportedly consumed recommended dosage of the individual products, the combination likely resulted in a greater than recommended dose of some constituents common to both preparations (but that is not known, either). The symptoms that are described are likely to be, at least in part, due to the combined ingestion. The dizziness, nausea, and sleeplessness are characteristic of relatively high dosage of ephedrine alkaloids. Distortions of seeing and hearing and shortness of breath are unlikely to be attributable to ephedrine and related compounds.

It is actually unknown whether or in what quantity ephedrine alkaloids were consumed at all in this case. The effects encountered were relatively mild and were quickly and fully reversible.

ARMS 11137

A 39 year-old female consumed Natural Trim products, one thermogenic pill at 10:00 A.M. and at 4:00 P.M., as directed (also took a vitamin pill and a booster pill at 10:00 A.M.), for 6.5 months. While being treated with antibiotics for a sore throat, she developed an upset stomach and stopped taking the products. She became shaky, weak, and exhausted, and felt as if she were "about to pass out if she tilted her head." Upon seeing her physician, she was diagnosed with hyperthyroidism and "subacute thyroiditis".

Obviously, since the described effects occurred after discontinuation of the ephedrine product, they are not acute effects attributable to it. While weakness, shakiness, and exhaustion may be subjective feelings associated with discontinuation of chronic use of stimulant compounds, such discontinuation is unlikely to be a major contributing factor in this case. First, the subject did not consume sufficient dosage of ephedrine alkaloids (according to self-report, and that is the only information concerning use that is available) to lead to such withdrawal phenomena. Secondly, she had two other medical conditions, infection of the respiratory tract and hyperthyroidism, both of which can provoke similar effects and both of which are more likely causes in this case.

ARMS No. 11140

A 59 year-old female used Power Trim and Power Prime. She reported suffering three attacks of vertigo, in 2/96, 4/96, and at an unspecified time. She went to the emergency room and saw her physician concerning these attacks.

Unfortunately, there is no information available, even self-reporting, of extent or duration of use, or of temporal relationship of use to the reported adverse events. Also, there are no medical records or opinions available concerning the reported events. Therefore, a critical evaluation of this case cannot be done.

According to the FDA Proposed Rule, Ref. 149a Table, Power Trim (obtained for evaluation relative to another case) contains 9.4 mg ephedrine and 1.8 mg pseudoephedrine per serving. There is no pharmacological basis for consumption of those doses causing vertigo as an adverse effect.

ARMS No. 11286

A 36 year-old female used Breathe Easy Herbal Tea on one occasion at less than recommended dose. She used it along with two Advil to relieve cold/congestion symptoms. Approximately 15 minutes after drinking tea she experienced rapid, pounding heartbeat. She felt so bad she could hardly get out of bed, but did not seek medical care due to anxiety about hospitals. Symptoms resolved completely within five hours. A routine medical visit one month later was unremarkable. Her medical history is significant for occasional palpitations.

There is no documentation of usage or of the adverse event beyond the subject's self-report. Ephedrine alkaloids can induce rapid, pounding heartbeat, but it is not known that the subject actually consumed ephedrine. Furthermore, she had experienced similar symptoms in the past with no identifiable cause. It is unclear whether or not ephedrine was involved in this mild adverse event.

ARMS No. 11401

A 42 year-old male used Energy Now, three tablets, on two separate occasions. The first use was uneventful. With the second use, two weeks later, he experienced severe diaphoresis, blurred vision, shortness of breath, lightheadedness, and pounding chest pain within one hour of taking product. Symptoms lasted approximately 15 minutes and had resolved completely by the time he was seen in the ER. He was admitted to the hospital overnight for evaluation, all of which was normal. He smokes 1.5 packs of cigarettes per day.

There is no documentation of usage or of adverse event; there is only the self-report. The symptoms described could be precipitated by ephedrine alkaloids, but they could also be caused by many other triggers (including caffeine, nicotine, allergy). The fact that he had taken the same dosage without incident on another occasion diminishes the likelihood that this event was due to ephedrine. Whatever the cause, the adverse event was mild and quickly and fully reversible.

ARMS No. 11442

A 39 year-old female used Thermajetics Herbal Tablets-Green, three tablets twice daily, along with four other products included in the Herbalife Diet Plan. After three to four months on the plan, she began experiencing blurred vision and headache. Two weeks later she began experiencing dizziness, lightheadedness, slurred speech, and numbness on the right side of her body. Evaluation by a neurologist indicated patchy sensory deficit in the right leg, most pronounced in the foot. MRI of the brain showed findings "consistent with recent hemorrhage associated with cavernous malformation. Further evaluation by an internist indicated no additional significant findings. Symptoms improved after subject discontinued use of the products.

There is no additional documentation of usage or of medical records available, so a complete evaluation cannot be done. However, it can be concluded that ephedrine is highly unlikely to be a precipitating factor in this adverse event for two reasons. First, it is unlikely that a dramatic acute event such as intracerebral hemorrhage would be caused by an exposure that had been continuous and unchanging every day for between three and four months. Secondly, the quantity of ephedrine in the Thermajetics Herbal Green Tablet is trivial (trace to 1.8 mg ephedrine per serving, according to Ref. 149a Table, sample from another case.) Such a small amount of ephedrine could not cause a sufficient rise in blood pressure to trigger a hemorrhage. For these reasons, the hemorrhage was undoubtedly precipitated by some other coincidental cause.

ARMS 11619

A 35 year-old female used E'OLA AMP II Pro drops for one day (time unspecified). She awoke at 3:00 A.M. on the morning after use with right-sided facial weakness, chest pain, palpitations, right arm weakness and numbness, photophobia, and unsteady gait. She was seen by a physician and entered the hospital. Symptoms improved during an uneventful hospitalization. All test results were within normal limits except cerebral arteriogram findings which suggested "mycotic aneurysmal change or possible changes secondary to an unusual drug-induced vasculitis or collagen vascular disease. Discharge diagnoses included: right facial and arm weakness, cause uncertain; improving right eye irritation; resolving headache; resolved chest pain and palpitations with negative workup; and history of right C5-6 cervical radiculopathy, carpal tunnel syndrome. Symptoms continued to improve during month after discharge. History is significant for: classical migraine headache associated with right jaw tingling; cardiac murmur with prior evaluation; and habit of drinking 1.5 quarts of caffeinated soda daily.

Analysis of the product used indicated that each serving contained ephedrine 13.3-18.5 mg, pseudoephedrine trace to 1.8 mg, and total ephedrine alkaloids 15.1 to 18.5 mg. No additional documentation of consumption or medical records were available.

Among the milder events reported, ephedrine in the doses apparently consumed, could have contributed to the headache and palpitations. The reported high intake of caffeine could also add to these effects and is likely to be a greater contributor to them than the ephedrine, since the onset of symptoms was relatively far removed (probably approximately twelve hours) from the dose of ephedrine and there had almost certainly been later ingestion of caffeine.

The more serious effect, the "unusual drug-induced vasculitis", is a theoretical effect rather than a proven one. If this did occur, it

would indeed be an unusual type of effect. Although it seems doubtful that ephedrine would produce such an effect, the possibility cannot be ruled out completely.

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